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President's Address

REFLECTIONS ON MEDICAL PRACTICE

BY

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Within my lifetime medical practice has been completely transformed. Progress in fundamental science and the development of technical skill in its application have changed the whole aspect of the venerable structure of empirical medicine which I explored as a student, and radical reconstruction has been necessary in many directions. It is not of these things, however, that I propose to speak on this occasion. The new knowledge, the new drugs and techniques, enable us to do much more for our patients: these things make our lives more interesting and satisfying, and we are grateful if at times uneasily aware of the difficulty of keeping pace with all of them.

My purpose is to direct attention to the increasing responsibilities that society imposes upon its doctors and to examine some of the consequences that may flow from a wider range of medical activity.

A Duty to Society

Early in the nineteenth century Jeremy Bentham conceived the idea that medicine had a duty to society as well as to individual patients, and he is the spiritual father of Preventive Medicine as it was developed by Thomas Southwood Smith, Edwin Chadwick, and John Simon. Despite their work it was not until 1899 that an Infectious Diseases Notification Act was approved, and it is salutary to recall the spirited resistance to it from those who believed that it infringed the passage in the Hippocratic Oath which proclaimed that whatsoever a doctor saw or heard in the course of his profession should not be published abroad.

Although the opposition to the notification of infectious disease now seems to us a little peculiar it was probably based on the same jealous, but not unhealthy, instinct to preserve the traditional relationship of confidence between a doctor and his patient that has stimulated criticism of much medical legislation in the past fifty years. However that may be, there is now no doubt that a doctor in clinical practice encounters types of responsibility which were never contemplated by Hippocrates, nor by the statesmen who advised her late Majesty Queen Victoria. His primary and ineluctable duty to ensure the best possible investigation and treatment for his patient remains, but, in addition, he must often decide whether or not the issue of a certificate is warranted to obtain pecuniary benefit from the State or to justify absence from work ; in many ways the doctor has become a custodian of part of the public purse, a sort of State almoner. Authority, not unnaturally, insists on supervision, so the cost of prescribing and the number of certificates become subject to comparison with the average of an area and a matter for inquiry if either appears to the Minister to be unreasonable.

It is not surprising that novel disciplinary checks of this kind caused resentment in many members of a profession bred in a long tradition of individual freedom, but I see no escape from them so long as a Welfare State remains the ideal of society.

We may justly plead, on the other hand, that administration should be flexible and tolerant and be guided by those who have first-hand knowledge of the difficulties and problems of practice. To a considerable extent, and particularly at certain levels, this has been achieved by the work of this Association and by the co-operation of doctors in the activities of executive councils, regional boards, and hospital management committees. It is disconcerting nevertheless that a general impression prevails that problems of policy tend more and more to be determined by officials in the Ministry of Health who know little of the stress of clinical work and less of the human problems inherent in it. Is it improper in me to suggest that those in official positions at the Ministry might be refreshed by quitting the shelter of Savile Row to share, from time to time, the perplexing duties of a doctor in clinical practice in hospital or in the home?

The Supreme Problem

But contemporary domestic difficulties, important though they sometimes seem, are trivial in comparison with the supreme problem that now confronts the world—the danger of atomic war. Four years ago Lord Adrian, in his presidential address to the British Association, said bluntly that our fate was now squarely in our own hands, and he stressed the urgent necessity for increased knowledge of how the mind of man could be influenced to avoid the catastrophe of conflict. With great authority he pointed out that it was not likely that the most detailed knowledge of brain

physiology would help mankind towards living more peacefully, though it might achieve clearer heads and a more even temper. Our knowledge of human behaviour is based on simple empiricism, and there is a clamant need for the branches of social science to make dispassionate studies of what actually happens in human societies. In Lord Adrian's judgment these large-scale investigations were too important a plant to be left in the hot-house atmosphere of research institutions and Unesco teams, and he made a plea for the recruitment of more social scientists in the universities and added the critical comment that their methods were not yet sufficiently objective and precise.

With all that Lord Adrian said I think we would agree, and when I read his speech I wondered whether medicine had not a duty to take some part in the study of the most urgent problem of our day and generation. For, surely, there is no group of men better equipped and more advantageously placed to contribute to this work than the family doctors of this country. They enjoy the trust and confidence of the vast majority of their patients: the nature of their work admits them to the most intimate aspects of family life, often over long periods of time. They are already aware of many of the motives that determine human behaviour in society, but their knowledge is rarely recorded in permanent form and dies with them.

For this misfortune there are several reasons. In the curricula of most medical schools little attention is given to the functions of medicine in relation to society. The dramatic success of scientific methods in the treatment of individuals appeals to the young, and in teaching hospitals absorbs their attention so exclusively that they tend to ignore that large part of clinical practice which is not measurable in terms of science and which often has no relation to organic disease. The recent revision of the Recommendations of the General Medical Council will enable Licensing Bodies to amend their curricula if they wish, but to avoid any misunderstanding I feel it necessary to say that for my part I would not sacrifice the rigorous discipline of fundamental science in the training of medical students, because it constitutes the firm foundation for future progress and stimulates a critical approach to the problems that confront us. Opportunity should be found, however, to encourage students at some stage to examine the wider functions of medicine in society.

Signs of Renascence

The principal factor that limits any activity by practising doctors in this direction may be simply stated. Most of them are too busy and lack the leisure that is essential to independent thought and fruitful investigation. Despite this difficulty there are signs of a developing renascence of family practice, and we should pay tribute to the remarkable achievements of the College of General Practitioners in recent years. I suggest to the members of that College that they should consider an approach to university departments of social science to examine the techniques that have been developed for the study of human behaviour and the methods for recording information in forms suitable for analysis and in the hope that co-ordinated research may be established.

When I submitted the first draft of this address to the Editor of the *British Medical Journal* he was good enough to send me a report from the *New Scientist* (June 5, 1958) of a lecture by Canon Raven as Visiting Professor of the Philosophy of Science at the College of Medicine of the University of Cincinatti, Ohio. I quote a passage: "I should like to see the province of medicine extended; I should like to see certain departments of the great profession equipped to study the diseases of corporate life. I believe there is room here for the application of precisely the same skills in diagnosis and treatment which the social worker does not have and which the medical man does. I am not depreciating the work of the social worker at all. But I am suggesting that between sociology and medicine there might well be established the same sort of unity which has been established between psychology and medicine."

Canon Raven was particularly concerned with such things as mass hysteria, the ethics of advertising, and the publicity which established enthusiasms with so little factual basis. These are large and important problems admittedly, but I doubt if they are the most suitable for first attempts in joint research. It might be better for us to begin with humbler topics, and I suggest a few at random.

Topics for Research

There has lately been considerable controversy about the eleven-plus examination. Some have contended that the success of a child in gaining admission to a grammar school when its brothers or sisters fail may lead to intense and disintegrating stress in a family, and for this reason plead that all schools should be comprehensive. Is it true? I believe that family doctors could well supply the information necessary for rational policy. What exact knowledge have we of the effects of the employment of married women on their children and their homes? And who could supply more reliable information than the doctors of those families? Does moderate consumption of alcohol and tobacco contribute to the peace and happiness of family life or the reverse?

In a recent book Lord Pakenham reviewed the evidence on which we base our opinions about the problems of juvenile delinquency and criminal conduct. He found that there was very little factual information on which we could rely: opinions were often conflicting and little was done to establish truth. Has not medicine something to contribute in this direction? Family doctors see the delinquent from his birth: they are familiar with his environment and often with his descent.

Study of these matters and many like them might yield information of great practical importance, and in my judgment we, as doctors, should welcome any opportunity to take part in them. To be of value, however, such studies must be serious and not casual, and I fear they are impossible for most doctors in the present conditions of practice. Lists are too large and leisure too restricted to permit sustained effort, but it might be possible for this Association and the College of General Practitioners to find ways and means to sponsor a preliminary trial of a scheme for joint research by a team of family doctors linked with a university department of sociology, and it would be an interesting experiment.

Adventure of this kind, a study of human behaviour in society, would surely restore interest in another problem of fundamental importance which we share with the whole company of thinkers and which medicine, absorbed in the application of its new therapeutic resources, has neglected of late. What is the nature of man? How should we regard the individuals who consult us?

It is a hundred years since Charles Darwin published *The Origin of Species* and about forty since we became aware in this country of the work of Sigmund Freud, and I am fully conscious, like William James, that every opinion must be forged in the face of stubborn and irreducible facts.

The Basis of Continued Life

The broad conclusion from biology is that man to-day is what he is as the result of evolution, natural selection, and the invention of conventional speech and of symbols such as numbers and formulae which not only record and store his past experience and achievement for the benefit of future generations but also bring order to his conceptual thought and enrich it in every field of activity—in literature, art, mathematics, and science. To that we may add that all life depends on green plants, including, of course, the algae of the seas, for they furnish the food of animals and so the nourishment of man. Plants alone seem able to fashion the stuff of life—proteins, sugars, and fats—from stable inorganic material in the air and soil with no other help but the light of the sun. This wonderful photosynthesis is the basis of continued life, and not unnaturally it has been studied diligently. What seems to be emerging is that there

are chemical and physical phenomena common to the activity of plant, animal, and human cells, and much that is now mysterious will become clearer when we know more of the exact role of nucleic acids in living processes.

Man, it seems, is one with nature—not merely with the organic nature of plants and animals but also through photosynthesis with the inorganic world—he has emerged from it and belongs to it. Fifty years ago that opinion had little to support it. Physics and chemistry then were widely separate subjects and there was a gulf between the organic and the inorganic. Pasteur in the 1860's had shattered the hypothesis of spontaneous generation, and we believed that all living things came from living forebears. So, indeed, they do. But was it ever so on this planet? The atmosphere in which we now live is very different from that which surrounded the earth when it first revolved upon its orbit, and it is conceivable, nay almost probable, that conditions may then have favoured the formation of the protein molecule, the stuff of life, from inorganic material in a manner that would be impossible to-day. The identity of man with nature I do not find discouraging; he remains a manifestation of the creative energy that formed the cosmos, and each of us may be, as Rupert Brooke thought, a pulse in the eternal mind, no less.

If we admit the truth of that opinion, are we committed to the belief that all human conduct is determined by forces beyond the control of the individual; that we are passengers in the evolutionary car and have no say in its direction? The irrefutable facts to which I have referred suggest it may be so, and to these might be added the evidence from genetics, for it seems certain that the limits of personal potential are set by genetic constitution, though accident and environment may restrict or encourage its development.

Human Behaviour

Has clinical experience anything of value to add to the discussion of this problem? There are facts in medicine that appear to support the full determinist position. As physicians we are familiar with the disorder of behaviour and the deterioration of character that are a consequence of acquired pathological lesions or inborn errors of constitution, and we are tempted at times to believe that human personality depends solely on physical conditions. But the fact that in some cases disease overwhelms or distorts an individual does not prove that personality is determined by physical processes alone. On the contrary, is it not general experience that patients show an astonishing variety of attitude and response to illness? Many who are crippled by injury or disease radiate happiness and energy and accomplish much, while others in identical conditions give up the struggle and become a burden to themselves and their kin. This is the common stuff of our daily work, and surely it encourages a belief that free will and courage are not illusions and that to each of us falls the duty of choice in our behaviour. The Freudians to account for such variation in conduct invoke the subconscious, but, important as that may be, I am still persuaded that conscious resolution plays as large if not larger a part.

It may be argued, justly, that research by scientific method is still in its infancy and that as it proceeds it will win knowledge of material processes that determine human behaviour. Equally true is it that research may also reveal much about the self-conscious human individual which defies explanation in measurable terms of matter: the curious sense of guilt, for instance, and the inhibition which have no parallel in animals.

Whatever the future may hold I think it is fair to say categorically at the present time that our scientific knowledge does not warrant the assertion that human life is entirely determined by physical factors, though their influence is great, and our daily work as doctors intimates the existence of free will and the capacity for choice, which in some inexplicable way have "emerged" in the course of the evolution of a self-conscious human being.

My friend Professor Roy Pascal, with whom I discussed this matter, reminded me of *Dichtung und Wahrheit*, the autobiography in which Goethe made a determined effort to define the factors that had influenced him and made him what he was. At first he seems convinced of the dominance of the material: he even says at the beginning that if he had been born a year or two later he would have been a different man. Yet as he proceeded he became more and more impressed by the unpredictable element in his personality and life. In the last book he refers to it frequently. He calls it the "daemonic" element which surged up within him, involuntary and unaccounted for. "It was like chance, since it evinced no sequence of causality: it resembled Providence, for it hinted at coherence."

Conclusion

If, as I believe, we may properly at the present time act on the assumption that man is something more than a completely determined animal, an important conclusion about medical practice follows. The relationship between doctors and their patients is deeper than that entailed by the solution of scientific and measurable problems: it is in truth a personal relationship in which intuition, sympathy, and compassion play a considerable part. To avoid any misunderstanding let us acknowledge that most of the manifest achievement of recent years has been due to distinguished work in basic and clinical science, and that it is our responsibility to encourage all such work and to accept its verified conclusions, but we must never forget the large part of clinical practice which depends on qualities that science cannot yet measure and possibly never will.

Our duty is clear; we have to put at the service of the patient, when it is necessary, all the resources of scientific investigation and treatment, but, in addition, we have to maintain in him the personal interest and concern of a friend.

SITTING, STANDING, AND WALKING*

BY

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It must be clear that what has so far been said about the orientation of the body when attempting to sit might well be repeated for standing, and indeed for any activity in which the individual desires to assume a definite relationship with and towards the outside world; there is therefore no point in repeating all this to serve the same purpose. I propose, therefore, to consider the mechanism of standing upright and how this is upset in such interesting syndromes as the drop attack and syncope.

As in any postural activity, the peripheral mechanism is primarily of reflex order—simple stretch reflexes which are modified by the afferent nerves from neck muscles, vestibular organs, eyes, and so on. It is of interest to mention the important driving function of the muscle spindles and the so-called servo mechanism described by Hammond, Merton, and Sutton (1956), who have given a far-reaching explanation of continued smooth-muscle contraction at the tonic level and the part played by the cerebellum in this mechanism. This is discussed below, after some of the clinical cases have been considered.

*The second of two Oliver Sharpey Lectures delivered before the Royal College of Physicians of London on February 11 and 13, 1958. The first lecture appeared last week at p. 63.

Case 6

The first patient to draw my interest sharply to the sudden failure of the upright posture was a young soldier who was digging a slit-trench. The sudden noise of a passing aircraft upset him and he looked up to make sure it was not a dive bomber—for it was in the days when dive-bombing occurred. He fell at once into the trench. He soon picked himself up, apparently mildly confused, for he attacked the man next to him—very inefficiently—as he felt he had been struck down. He said he thought he had been hit on the back of the head or neck, and that it was for this reason that he had fallen. He was uncertain whether he had lost consciousness, but did not remember hitting the ground.

Full examination and investigation showed that he had a moderately large ependymoma of the fourth ventricle, and I interpreted the sudden falling or drop attack, as it may well be called, as due to sudden medullary compression producing loss of function in that vital region, rather than to a blockage of the flow of cerebrospinal fluid producing an acute hydrocephalus, as is said to occur in colloid cysts of the third ventricle. I did not attempt to decide how the loss of function occurred or to what the fall was due.

Case 7

Some four years later I saw a young man with this story. While running through a bulkhead opening on board ship he struck his head on the low beam and fell sharply to the ground. He remembers that his legs tingled a bit, but he soon picked himself up. He felt a little odd but thought this was due to the blow on his head, though he admits it was not very severe. The same thing happened a second time while playing some deck game. He again ran through an opening, struck his head, and once again fell to the ground and his legs tingled for a short time. This occurred on a troopship, and his companions were so intrigued that they tried the dangerous experiment of pressing on the top of his head. He said that this made his legs tingle and fold up. Fortunately they didn't try this more than twice, and seemed content to achieve a minor response. He was sent to hospital, and there I found that he had a mildly stiff neck and a very minor paraparesis with increased deep reflexes and equivocal plantar responses. There was no sensory change. In his previous history it appeared that while at school, aged 12, he dived into the shallow end of the swimming-pool and struck his head forcibly on the bottom. He was rendered powerless, but was pulled out and carried to bed. There he lay for 10 days unable to move or feel his legs, and with very feeble arms. He improved, however, and in four weeks was up and about, soon playing games, though with a stiff neck that lasted some months. According to the patient at no time were any investigations carried out.

On admission *x*-ray examination showed that he had an old fracture-dislocation of the odontoid peg which was rotated so that it lay at right angles to its former position with its apex pointing to the lower medulla. Tomograms showed that the medulla and upper cervical cord would have to carry out a considerable bend in order to negotiate the top of the odontoid. It was clear that each time he struck his head the violent impact squeezed the medulla and caused a failure of function, and the legs gave way. Close questioning disclosed no loss of consciousness or something so brief that the patient did not remember it.

Case 8

Some two months ago I saw a 30-year-old man who for two years had been having difficulty with his legs. They had become increasingly weak and he would tend to fall. In the last year he fell often, and if, as was usual, he pulled his head back to avoid striking his face on the ground, then his feet would get much weaker and fail to carry his weight, and if he were picked up he would fold up again. Usually he would ask to be left alone, and after three or four minutes he would regain enough power to pick himself up and walk on. He said that if he put his head back voluntarily then his lower back and legs would tingle and his feet and legs would get weak so that he could not remain standing. Naturally, he never voluntarily carried out this manœuvre long enough to produce falling. In its essence this case sounded very like that of the young man with the fractured adontoid; but, as this was 12 years later, I was able to plan some clinical investigations.

Straightforward examination showed that he had no abnormalities in the skull, but his neck could not be extended more than 10 degrees from the vertical before bringing on the tingling, which I suppose might be called the reversed electric sign of Lhermitte. There were no abnormal findings in the upper limbs. In the lower limbs there was a moderate spastic weakness with increased knee- and ankle-jerks, bilateral plantar responses, and about a dozen beats of ankle clonus. Sensory testing showed only a very minor impairment of sense of passive movement in the toes and of vibration sense on the feet, approximately equal on the two sides.

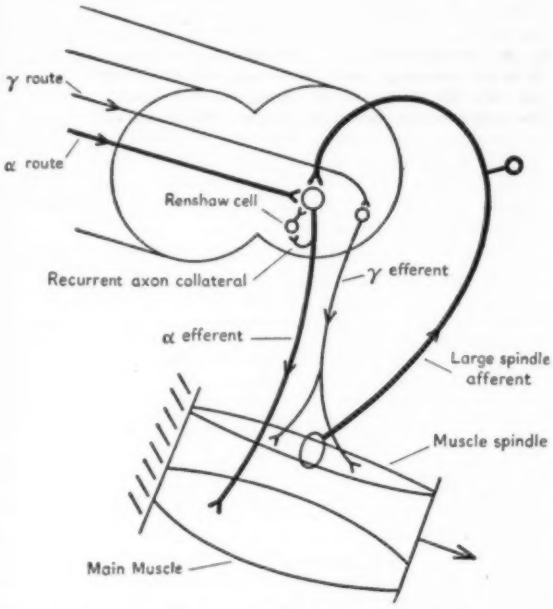
The experiment consisted merely of extending the neck so that tingling was just produced. The only change on examination, which of course had to be rapid, was of a slight depression of touch sensation in the feet. Whether this was genuine depression or merely due to the interference produced by paraesthesiae I cannot say. That ischaemic and post-ischaemic paraesthesiae interfere with sensory testing is well known, and the same may have been happening here. Gently and cautiously the head was taken a little further back. The patient was unaware of anything much happening except an intensification of his paraesthesiae, but his voluntary power was definitely impaired at the ankle and knee—mainly in the dorsiflexors and extensors and also, though not so much, at the hips—again mainly in the extensors. I must stress that this was all done hurriedly—that is, in a short period of time—and that no accurate measurements of power were made, but I had no doubt there was a real difference of power, and the patient had no doubt there was diminution. The deep reflexes remained brisk as before and the plantars were extensor, but tone was very definitely reduced, and the ankle clonus was abolished. Sensory testing showed further increase in the cutaneous impairment to touch and also for two-point discrimination, but the paraesthesiae had increased also.

All these results were confirmed on several occasions. The main point which emerged was that coincident with the onset of weakness there was a profound diminution of tone as estimated by the sense of resistance to passive stretch. Yet the deep reflexes and plantar responses were unaffected. This patient had a compressive lesion extending through the foramen magnum.

The Drop Attack

Here, for the first time, so far as I was concerned, appeared a possible explanation of the drop attack—that it might be due to a cessation of postural tone in the lower limbs. The weakness on voluntary movement was increased but did not appear sufficient to cause the sudden fall to the ground that occurs in the drop attack, the so-called idiopathic form of which is described below. On the other hand, there was the curious observation that the tendon reflexes remained as brisk as before and the plantar responses just as extensor. How can one reconcile these findings? Now, every clinical neurologist at some time or another has seen just such an apparently paradoxical combination and has had as much difficulty in explaining this as I had. Being brought up in the traditional school of neurophysiology which was developed by Sherrington, I believed that the deep reflex such as the knee-jerk was dependent on the degree of tone in the muscle stimulated—the more tone the greater the response, the less tone the smaller the response; in other words, that the deep reflex was a fractional stretch reflex. Yet here were tendon reflexes unaffected by the tone in the muscle. Definite hypotonia had been produced, yet the reflexes were as brisk as ever.

The answer has now been provided by the results of Merton and his co-workers in a series of brilliantly planned experiments both in animals and in man on the nervous control of muscular contraction (see Diagram). So important are these for a proper understanding of the drop attack and the paradoxically increased deep reflex in the hypotonic limb that I make no excuse for summarizing them here.



The muscle spindle lies in parallel with the main muscle and its fast conducting afferent is in synaptic connexion with the large α motor neurone supplying the main muscle fibres. A slow conducting γ motor efferent (thin line) supplies the contractile poles of the spindle and thus can alter the bias on the spindle sensory ending. The muscle can be made to contract either by impulses from higher centres exciting the α motor neurone direct (the α route) or by impulses in the γ efferents (the γ route) which activates the muscle indirectly via the stretch-reflex arc (the "follow-up" servo). A subsidiary feedback loop via the recurrent axon collateral and an inhibitory Renshaw interneurone may be concerned in stabilizing the response of the α motor neurone to its excitatory input. (From Hammond, P. H., Merton, P. A., and Sutton, G. G., *Brit. med. Bull.*, 1956, **12**, 214.)

A muscle is brought into action by motor impulses, but the degree of that contraction is estimated by sensory receptors in the muscle, and in the light of this information, called the "feedback," it modifies the rate of motor discharge. It is true that visual information may modify the motor discharge as may cutaneous impulses, but it is the muscle sense organs which play the major part in assessing or monitoring the performance of the muscles themselves.

The muscle spindles are the sensory organs of muscles. They lie among the main muscle fibres, having the same attachments and therefore altering in size with contraction or relaxation of the muscle itself. It must be remembered that the poles of these muscle spindles are contractile and receive very fine-fibred efferent supply, the γ fibres, whereas the main muscle fibres receive large or α fibres. The reflex connexions of the muscles are such that impulses set up by stretching the spindles excite the muscles' own motor neurones. Thus extension of the muscle results in an augmented contraction which tends to resist the extension. This is the stretch reflex of Liddell and Sherrington (1924). This has the properties of a closed loop self-regulating mechanism using information from the spindles to maintain a constant muscle length. It is clear that this has enormous advantages over a straight-through system in which posture is maintained by a steady stream of motor impulses without sensory modification or feedback, in that it automatically compensates for changes in load or for fatigue.

This type of stretch reflex would maintain a fixed posture well, but it is clearly inflexible and needs modification for ease of changing muscle-lengths while maintaining postural tone. This modification is carried out by means of the contractile poles of the muscle spindles. The sensory portion of the spindle lies between these poles, hence shortening the poles by impulses along the γ efferents will stretch the sensory spindle so that the stretch reflex will be activated just as if the muscle itself had been stretched. The muscle will then shorten reflexly until the increased rate of spindle discharge has been offset, and that will be when the muscle has shortened to the same extent as the contractile poles of the spindle.

Merton and his associates have named the loop mechanism of the simple stretch reflex the "length servo" mechanism and the modification next mentioned the "follow-up servo."

Experiments have, however, shown also that in deafferented limbs, in which this whole servo mechanism must be out of action, movements can occur without it: sudden movements almost invariably do through the α efferents to the muscle, and in further work Granit (1955) has shown that the cerebellum and associated structures determine whether the length servo or the straight-through mechanism is to be used in contraction. As Hammond *et al.* (1956) say: "This fits in with, and extends the current notion that the cerebral hemispheres decide what is to be done, and the cerebellum has the job of arranging how it is to be carried out."

We are now coming to the crux of the matter. There is evidence that even when the α route is used, the motor-neurone discharge is subject to servo control. Branches from the motor axons run back into the ventral horn and excite internuncial cells named after their discoverer, Renshaw (1941), which in turn inhibit the neighbouring motor neurones. It may well be that this mechanism provides the stabilizing influence on the motor-neurone pool. Certainly recurrent collaterals which might function in this way are to be found throughout the nervous system.

It has been shown that this Renshaw loop on the α fibres has an appreciable delay of some 2–5 msec., and therefore a brief afferent volley may pass through the loop while the sensitivity is high before the stabilizing influence of the collateral loop can be exerted; the tendon jerk gives just such a brief synchronous nerve volley and it need not necessarily be related to the status of tone in the muscle. In other words, the tonic mechanism is motivated through the muscle spindles and the γ efferents, the tendon jerk through the α efferents. The two are not necessarily related. The γ servo loop is under control from the cerebellum, and when the latter is put out of action this tonic mechanism will fail and hypotonia result. The brief synchronous afferent volley due to the tap on a muscle tendon will get through the motor unit pool and produce a brisk twitch, but the α fibre mechanism cannot respond as a tonic mechanism because of the controlling influence of the Renshaw loop. This comes into action too late to prevent the passage of the impulses necessary for a brief reflex response, but prevents a prolonged reflex response.

Considerable further evidence exists for the α and γ fibres in muscle. In 1919 it was shown by Liljestrand and Magnus that procaine injected into animal muscles abolished tone in the decerebrate state long before there was any alteration in either reflex response or that due to motor-nerve stimulation. In 1924 F. M. R. Walshe showed that injection of procaine into the muscles in Parkinsonism or spastic hemiplegia reduced the tone considerably but left voluntary power, if anything, rather better. This was interpreted by both authors as a selective knock-out of the afferents from the muscle. Recent work, however, has shown that the γ afferents are far more sensitive to procaine; and Matthews and Rushworth (1957a, 1957b) have found experimentally

that this is the probable explanation for the selective action in the previous authors' works.

A further most interesting finding indicating the separate nervous mechanism is that of Gilliatt (1954), who produced peripheral nerve ischaemia by means of pneumatic tourniquets. In patients with severe pre-existing spastic weakness the diminution of muscle tone following local ischaemia may outlast any increase in muscular weakness caused by the procedure, and patients report improvement in the mobility and usefulness of the limb for several hours. This must be due to a selective action on the efferent tonic mechanism; in other words, the γ fibres.

Here, if we accept this work—and I have not quoted all the compelling experimental evidence on which it is based—is an explanation which will serve for the paradox of the hypotonic limb with brisk deep reflexes, and here, I would like to submit, is the explanation for the drop attack.

Clinical Description of Drop Attack

The clinical description of such an attack is of a middle-aged individual who for no obvious reason suddenly falls where she stands. Most, though not all, patients are sure they do not lose consciousness. There is no warning, and they do not try to save themselves because the whole episode is so sudden. They often say that they fold up at the knees, and many women have complained about ruining their stockings at the knees, which certainly indicates a falling forward and might support the folding-up suggestion. Many of these patients rise almost as soon as they have reached the ground, without confusion or disturbance other than being shaken by the episode, though some may hurt themselves during the fall or, if frail and elderly, they may well be very shaken and dazed. All these patients are quite sure that they do not trip, that they felt well before the incident, that only their legs gave way, and that they can continue walking as soon as they are on their feet again. Physical examination and investigation of these patients rarely reveals anything of note to explain the happening.

On the basis of Cases 6 and 7 I would like to suggest that it is the lower brain stem which is the site of the dysfunction that produces the event. The nature of the possible lesions are discussed below, but the mechanism is probably best explained on the lines suggested by the physiological work of Granit and of Merton. Interference at brain-stem level, with the connexions of the cerebellum, deprives the postural-tone mechanism of the control by γ-fibre servo loops which go out of action. This causes a failure of postural tone, and the individual folds up and falls to the ground suddenly. The α mechanism cannot take over at such short notice, and in any case is not suited, as has already been shown, to the maintenance of steady postural contraction.

Case 8, in which we could fractionate the drop attack, gives every indication that this hypothesis is feasible if no more, for we were able to produce definite hypotonia yet the deep reflexes were brisk, the former indicating a diminution in γ activity, the latter the integrity of the α pathway.

Given the site of the syndrome, what could produce such happenings? My three opening cases indicate that this can occur with compression of the brain stem. In each of these cases, however, the condition was reversible, which is an important feature of the drop attacks, and it is probable that the compression acted on the vascular supply. In each case a special manœuvre to produce compression was necessary, and on reversing the process the condition was reversed. It is tempting to suggest that in most cases of this type of drop attack the mechanism is a transient change in the blood supply of the brain stem. There is some evidence that this may be so. In a recently described series of aneurysms of the vessels of the posterior fossa Dimsdale and Logue (1957) were very positive that weakness and collapse of the lower limbs were characteristic of the condition, while Williams and Grahame Wilson (1957) have shown examples of basilar atheroma in patients with the syndrome.

Syncope and Epilepsy

The other types of falling attack of major importance are, of course, those due to syncope and epilepsy, and these often need differentiation. The work of Sharpey-Shafer (1956a) has elucidated many of the mechanisms of syncope. He defines the condition as an acute decrease of the cerebral blood flow producing loss of consciousness. The rapidity of the decrease in flow determines the length of warning symptoms. In cerebral flow it is mainly the arterial pressure which is the governing factor, and when this falls below 50 mm. Hg for a few seconds syncope results. As the arterial pressure depends on the cardiac output and the peripheral resistance it is clear that a fall in either, or of both to a less degree, will be the mechanism involved. The compensating factors are the baroceptor reflexes which usually keep the cardiac output and peripheral resistance working in opposite directions.

The clinical varieties may be split into several groups.

A. Decreased Filling Pressure and Stroke Output

Normally the diminished output in the upright position due to diminished filling of the heart is compensated by the baroceptors, but standing for long periods on a hot day may cause overfilling of the lower veins and grossly decreased filling pressure, so that no amount of peripheral vasoconstriction can compensate for this and the individual faints. A rise of intrathoracic pressure as in the Valsalva manœuvre will cause acute decrease of filling, depending on the height of the intrathoracic pressure, especially if there has been a degree of previous vasodilatation as produced by the warmth of a bed or a bath. Similarly, coughing (Sharpey-Shafer, 1953a) in the powerful short-necked man may raise the intrathoracic pressure high enough to prevent adequate filling of the heart and so decrease output-producing cough syncope.

B. Decreased Stroke Output

This is best seen in the Stokes–Adams syndrome. Here it must be said that if the cerebral anoxia is prolonged enough the convulsion will occur together with voiding of urine.

C. Decreased Filling Pressure and Stroke Output with Vasodilatation

This is best seen in squatting (Sharpey-Shafer, 1956b), for in this state blood is pressed out of the veins of the legs and cardiac filling pressure rises. This gives rise to reflex vasodilatation. If one then stands erect suddenly the hydrostatic fall of filling pressure and cardiac output takes place while this vasodilatation is still present, and this may be sufficient for a few seconds to lower the arterial pressure to a syncope level. This in a minor form is a very common happening.

D. Nocturnal Fainting

These cases are labelled nocturnal, though they need not occur strictly at night. They are, however, given a separate grouping because they are relatively frequent and almost always raise the problem of epilepsy. Usually the subject gets out of bed during the night to empty the bowel or bladder. In the normal person just getting out of bed alone usually has no effect, for the baroceptors respond very rapidly and constrict the peripheral resistance, thus countering the vasodilatation produced by the warmth. If for some reason the baroceptors cannot act, then this compensation cannot occur and fainting will result, often quite suddenly on assuming the erect position. Failure of baroceptors can occur because of the effective use of ganglion-blocking drugs which break the efferent part of the pathway; extensive sympathectomies would do the same. Sharpey-Shafer (1953b) has shown that the pathway can be blocked on the afferent side of the baroceptor reflex in diseases of the nervous system, such as tabes dorsalis. If after the subject jumps out of bed he empties the bowel there may be sufficient straining to constitute a Valsalva manœuvre, and this, associated with the warmth vasodilatation, may be enough to cause syncope.

Standing to empty the bladder at night may produce syncope by another mechanism. My attention has been drawn to the pressor effect of the distended bladder by my colleague Dr. Roger Gilliatt. This was shown in patients with spinal transection (by Guttmann and Whitteridge, 1947), when distension of the bladder could give a blood pressure well over 200 mm. Hg. It may well be that, modified perhaps, this is effective in the whole man and that emptying the bladder reduces this pressor stimulus while the rest of the body is in a state of vasodilatation produced by warmth, and in the upright position may well lower the arterial pressure to a syncopal level. There is no doubt that those of us who see many "fitters" and fainters are bound to see a fair number of cases that occur at night in these circumstances.

E. Reflex Fainting

This can be emotional or produced by pressure on the carotid sinus or the eye—the oculo-vagal reflex of Gastaut and Fischer-Williams (1957). In the former the characteristic feature is an acute peripheral vasodilatation taking place in the muscles, but there is associated pallor of the skin suggesting that the cutaneous capillaries are intensely vasoconstricted. With this there is a preceding gasp, a feeling of uneasiness, and nausea, and then the features of cerebral anoxia supervene. Sharpey-Shafer (1956a) points out that in fact there is a decrease of cardiac filling pressure before the vasodilatation, and postulates that owing to the decrease in filling pressure the afferents in the heart are stimulated, which then sets off the rest of the reflex. Bradycardia occurs after the vasodilatation, and it is clear that the compensating reflexes are temporarily out of action. The intense vasoconstriction of the skin is due in part to liberation of the posterior pituitary vasopressin, and the skin may remain pale for many minutes after the attack and large amounts of the hormone may be found in the urine after either an emotional or a haemorrhagic faint (Taylor and Noble, 1950). It is interesting that patients with heart failure do not faint—which is attributed to the continued maintenance of the cardiac filling pressure.

Carotid sinus and ocular-vagal reflexes produce their effects by cardiac slowing or arrest and not by vasodilatation primarily. Where vasodilatation occurs it is due to the baroceptors having been overcome. In Stokes-Adams attacks peripheral vasoconstriction is usual, as can be seen by the overswing of the arterial pressure during recovery.

The work of Gastaut and Fischer-Williams (1957) is most interesting in their attempt to separate syncope from epilepsy. They used the oculo-vagal reflex—that is, firm pressure on the eyeball—to induce syncope which resulted from reflex cardiac inhibition. They studied 100 patients who had had one or more attacks of loss of consciousness in association with pallor, sweating, nausea, malaise, and sometimes convulsions resembling grand mal, but in whom the resting E.E.G. was normal. They recorded the electroencephalogram, the electrodermogram, which measured the amount of sweating on the forehead, and the electrocardiogram.

They observed two types of syncope—the immediate and the delayed. The immediate occurs within one to five seconds of ocular compression and is due to reflex vagal inhibition of the heart. Delayed syncope may occur from 20 to 70 seconds after the compression, when the most important factor is vasodilatation with fall in blood pressure, though bradycardia or cardiac arrest may occur at the same time. These two forms may occur separately or follow one another in the same patient.

When cardiac arrest lasted three to six seconds there were no clinical or electrical abnormalities, but there was some desynchronization of the E.E.G., which is the usual finding with pain of any kind, and there is no doubt that ocular compression is painful. When cardiac arrest lasts about 7 to 13 seconds slow waves appear in the E.E.G., usually but not always associated with disturbance of consciousness. These slow waves have no resemblance to epileptic waves. The relationship of the slow waves to loss of consciousness varies from patient to patient: sometimes there may be complete unconsciousness from the beginning; sometimes there may be a minor absence only. If cardiac arrest lasts more than 14 seconds there is always complete loss of consciousness and then one or two myoclonic jerks. Following this the patient suddenly develops an intense generalized tonic spasm in extension with opisthotonos looking like decerebrate rigidity or a tonic posterior fossa fit. If the tone is different in the two sides then lateral deviation of the head may occur. During the time of the tonic phase the E.E.G. is absolutely flat with no rhythms appearing at all. The spasm lasts 10 to 20 seconds, and during this time heart beats reappear. Even if they appear at the beginning of the tonic spasm they do not prevent its evolution; once initiated it must go on to completion.

As soon as the spasm is over, slow bilateral large waves appear in the E.E.G. and again a myoclonic jerk may be found. This lasts 24 to 30 seconds. The rhythm takes several minutes to reach normality, however, and during this whole period the patient feels odd and faint. The loss of consciousness is certainly due to cerebral anoxia coming on rapidly owing to asystole in these patients, and the critical period of asystole is about 14 seconds. The tonic spasm in the seizure is regarded by these workers as due to a liberation of the reticular substance in the brain stem from the control of higher structure, together with a possible anoxic stimulation of the reticular substance itself. The flattening of the E.E.G. is interpreted as a cessation of function in the cortex which spreads downwards to involve all structures until the reticular substance is reached, where increased activity takes place. This has been shown also in experimental animals (Ward, 1947). Slow synchronization of E.E.G. rhythm which follows is due to a recovery of the higher structures.

Gastaut and Fischer-Williams go on to analyse the difference between epilepsy and syncope with convulsion. They suggest that the tonic phase in both syncope and epilepsy is due to a similar overaction of the reticular substance in the brain stem. In syncope this is due to the cerebral anoxia causing cessation of function above this level with liberation of the lower structures, which may also be directly stimulated by the anoxia. In epilepsy the brain as a whole is functionally active, as can be seen by the abnormal rhythms in the E.E.G., and it is this epileptic activity which, occupying the brain as a whole, allows the liberation of the reticular substance to produce the tonic phase. The clonic phase of epilepsy is due to attempted inhibition produced in the cortex breaking up the tonic phase. This is impossible in syncope because the higher parts of the brain are functionally dead owing to the precipitating cerebral anoxia. This is an attractive hypothesis, but it still needs some further proof. Gastaut and Fischer-Williams make it quite clear, however, that on E.E.G. studies and on clinical inquiry syncope should be distinguishable from epilepsy. Some of these observations have been made before, though not the same interpretation has been put on them.

An intriguing example is given in the discussion which took place at the Royal Society of Medicine in 1950 on "fits and faints." This case was quoted by Symonds (1950), though the observations were made by Ashby and Denis Williams. The patient was referred as a case of epilepsy by a doctor who was an eye-witness of an attack. In hospital he had an attack, when the pulse stopped completely for 45 seconds. After ten seconds he had a fit, with rolling eyes, rigidity, and a few convulsive movements. In a subsequent induced attack the E.E.G. showed no epileptic activity. This, it must be admitted, is a very similar observation to that of Gastaut and Fischer-Williams. It makes the differentiation between fit and faint both easier and more difficult, for, apart from the E.E.G., the important difference is that of the presence of a true clonic phase in epilepsy, whereas in syncope only a minor myoclonic jerk may be seen. Most neurologists have been brought up on the classical writings of Gowers (1901, 1907) on epilepsy and have believed that frequent and chronic fainters will usually turn out to be sufferers from epilepsy. In fact, Gowers says that "if a patient faints often enough he is sure to have a fit some time." If this new work is accepted, then we must surely alter this sentence to, "If a patient faints often enough he is likely to have a tonic fit sometimes, perhaps an epileptic fit never."

Walking

We now come to walking, which I will deal with very briefly because it is again compounded of the various phenomena already discussed. We find that to walk straight requires the ability to stand straight and to transfer the weight from one leg to the other without any disturbance of equilibrium.

To walk accurately requires also a knowledge of where one's legs are, otherwise they go in the wrong direction, trip one up, and generally misbehave in a way that makes progression a hazardous process.

There must also be an effective mechanism to give information which will grade the amount of muscular contraction necessary to give a smooth performance. Of course, all this has to take place for artificial legs as well as for natural ones.

I saw a 50-year-old man who had a lower limb removed in the mid-thigh region for Buerger's disease. I had to see him for some trivial neurological condition while he was convalescing from this operation, and I saw him subsequently from time to time for the same reason. He was provided with an artificial limb, and eventually he learned to walk moderately well with this. He was brought to my out-patient clinic one day because of an attack—clearly a cerebral thrombosis—which had affected the arm on the side of his amputation. He had minor weakness only, but a moderate sensory loss affecting all modalities and making his hand very clumsy. He said he didn't know where it was or what it was doing. In fact, he now had the greatest difficulty in walking. One could, I suppose, argue that he had lost the sense of position in the artificial limb; which sounds absurd, although no more absurd than the amputee who suffers from chilblains on the toes of the leg which had

been lost. The clue was provided by the patient saying that after the stroke he had lost his phantom leg. This is the patient I mentioned in the first lecture as resembling the patient of Head and Holmes (1912) who lost his phantom after a parietal vascular lesion. From this patient it would appear that to walk adequately one must know the position of the limb in space, and, if one is walking on an artificial limb, then it is only effective if it is possessed by a phantom leg which supplies it with the knowledge that is necessary to make it function as a limb rather than just as a support, and an inefficient one at that.

The ataxic walk of the individual with severe cerebellar disturbance must be due in part to the inefficiency of the automatic grading of muscle effort produced by the disorganization of the γ fibre mechanism as already suggested in an earlier part of the lecture, and the use of the more forceful, but uncontrolled α fibre system, so that improper force is used. If one watches the feet of a patient with inadequate cerebellar control it is possible to see constant contraction and relaxation of the foot muscles going on, so that the toes are clawing into the ground—again this is due to the use of a nervous control not designed for the purpose.

There is, however, another side to cerebellar control, and that is equilibration. For it is possible to have the cerebellum so disorganized in its older part—the flocculo-nodular lobe which forms the greater part of the roof of the fourth ventricle—that there may be gross disorder of equilibration. The patient staggers violently from side to side and is quite unsafe on his feet. Yet on formal testing for cerebellar ataxia as in the heel–knee–shin test there is no disorder. This is because the control of the γ system is intact.

It is remarkable how difficult it is for the patient with a severely damaged cerebellum to compensate alone—how simple it is for the compensation to be effected by another. The patient who can walk only with a stagger from side to side may, if he links an arm with a normal person, walk reasonably well. I have seen such a patient do ordinary relatively sedate ballroom dancing apparently so well and so disproportionately to his ordinary walk that he came labelled as a hysteric.

It appears, therefore, that for the equilibration difficulty sufficient stabilization can be provided by another person, but only so long as the γ system is intact. I remember Riddoch demonstrating this with great verve and ending the demonstration by saying that "clearly one cerebellum was enough for two."

Fatigue

I am brought finally to a few words on fatigue in muscle performance, as in walking or in running. At one time the theory of fatigue in profound effort was attributed to fatigue in the central nervous system, but it has been shown that this is inaccurate, and that fatigue is a peripheral phenomenon due to the failure of the circulation to remove metabolic products of muscular contraction. This is easily demonstrated by fatiguing a limb and arresting the circulation at the moment of cessation of muscular contraction, when there will be no recovery of power until the circulation is established. This is evident as applying to severe effort, as when doing heavy muscular work, but it is also the case for skilled fine movements. It was found experimentally that in skilled tasks, even in the lightest such as writing, the muscles are often working nearer the limit of muscular endurance than is imagined, but that owing to the muscles' proprioceptive servo control fatigue is compensated for automatically until considerable fatigue occurs, when the muscle will suffer a relatively sudden breakdown in its performance.

Conclusion

I have dealt with certain aspects only of the means by which we sit, stand, and walk. These lectures have been really a consideration of not sitting, not standing, and walking very badly, but it is only by study of the dissolution of such processes that we can ever hope to elucidate the means by which we manœuvre ourselves into a desired posture as when sitting; the means by which we maintain it, as when standing; and the means by which we co-ordinate all our muscular activity and keep the muscles contracting without overdue fatigue, as in walking.

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HAEMORRHAGIC THROMBOCYTHAEMIA

REPORT OF TWO CASES TREATED WITH RADIOACTIVE PHOSPHORUS

BY

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Epstein and Goedel (1934) first suggested the term "haemorrhagic thrombocythaemia" for the bleeding disorder which is characterized by a persistently raised platelet count. Although bleeding accompanying thrombocytopenia is commonly seen in hospital practice, the association of haemorrhage and thrombocythaemia is extremely rare, and probably no more than 30 cases have been reported in the world literature. Fanger *et al.* (1954) reviewed 28 cases of thrombocythaemia, but in six of them haemorrhagic manifestations were not present. Hardisty and Wolff (1955) analysed the clinical and haematological features of 18 reported cases of haemorrhagic thrombocythaemia plus a further five of their own. Of these 23 patients, 19 were over the age of 40 and there were almost equal numbers of males and females. Bleeding most commonly occurred from the nose and alimentary tract, and,

although bruising was not uncommon, purpura was rarely observed. Blood loss invariably resulted in a hypochromic anaemia, and all cases showed a raised platelet count and leucocytosis.

In addition to bleeding, patients with haemorrhagic thrombocythaemia may have thrombotic episodes. Presumably, these are closely related to the excessive number of platelets, but the mechanism of the bleeding is unknown. Approximately half of the reported cases showed abnormal bleeding-times; otherwise the standard tests of haemostatic function were normal. Hardisty and Wolff (1955) found a qualitative deficiency of the platelets in their five cases, as evidenced by their behaviour in the thromboplastin generation test, but were of the opinion that this was not the only factor involved.

The object of this paper is to present clinical and haematological details, including investigation of the blood-clotting mechanism, of a further two cases of this rare bleeding disorder and to report the beneficial effects of treatment with radioactive phosphorus (^{32}P).

Case 1

A road-worker aged 58 was referred to the department of surgery of Leeds General Infirmary on October 9, 1956, because of chronic bleeding from the alimentary tract for at least six years.

A history was obtained of good health until 1944, when he began to have attacks of abdominal pain. They were at first infrequent, and he was not seen at hospital until April, 1950, when he was found to be anaemic and tender in the epigastrium and right iliac fossa. Occult bleeding from the bowel was detected, and blood examination showed: haemoglobin, 8 g./100 ml.; red cells, 3,410,000/c.mm.; colour index, 0.79; white cells, 16,400/c.mm. (polymorphonuclears 74%, lymphocytes 23%, monocytes 3%). Radiological examination of the alimentary tract failed to reveal any source of bleeding. A diagnosis of peptic ulcer was considered most likely, and treatment of the anaemia with oral and later parenteral iron was advised.

In November, 1950, tonsillectomy was carried out. A good deal of haemorrhage occurred and a bleeding point had to be ligated.

During the following six years he was admitted to various hospitals on numerous occasions because of recurrent alimentary bleeding. Investigations carried out during this period revealed a chronic hypochromic anaemia with leucocytosis, but repeated radiological examinations of the alimentary tract, gastroscopy, and sigmoidoscopy failed to reveal a source of haemorrhage. In April, 1953, a laparotomy was performed, but no abnormality of the stomach, duodenum, small gut, liver, gall-bladder, or spleen was observed. The possibility of a bleeding disorder was apparently not considered, and there is no record of a platelet count having been done, although in 1955 a blood film was reported as showing abundant platelets.

During 1956 the bleeding became more severe and he was admitted to hospital for blood transfusions on eight occasions between January and September. In October a second laparotomy was performed (Professor J. C. Goligher). The stomach and duodenum were explored, but they contained no obvious blood. The jejunum and ileum also looked normal, and blood was first encountered in the terminal 2–3 ft. (30–60 cm.) of the ileum. Blood was also present in the colon, but no source of haemorrhage was discovered. The liver and spleen looked normal. Repeated blood transfusions were necessary post-operatively, and, in addition to melaena, epistaxis and haemoptysis occurred. On October 24, haematological investigation was requested.

Physical examination showed only anaemia. Blood examination gave the following results. Blood group B, Rh positive; haemoglobin, 6.8 g./100 ml.; red cells, 2,620,000/c.mm.; reticulocytes, 1%; mean cell volume, 89 cubic microns, mean corpuscular haemoglobin concentration, 29%; E.S.R. (Westergren), 21 mm. in the first hour. Platelets numbered 2,110,000/c.mm. and the platelet layer in the haematocrit tube measured 11 mm. The bleeding-time was five minutes (Duke), and Hess's capillary resistance test was negative. White cells 73,600/c.mm. (metamyelocytes 1%, neutrophils 89%, eosinophils 2%, basophils 1%, lymphocytes 4%, monocytes 3%). The blood film showed hypochromia and target cells were present. Bizarre forms of platelets, abnormal in shape and size, were present. Fifteen nucleated red cells per 100 white cells were observed, but no megakaryocytes were seen in the peripheral blood. Sternal bone-marrow aspirate was hypercellular, and erythropoiesis and granulocytopoiesis were normal. Mature megakaryocytes were abnormally numerous and surrounded by sheets of platelets. Many immature forms were also present (Fig. 1).

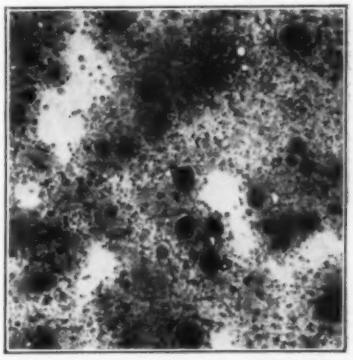

FIG. 1.—Case 1. Bone-marrow film from sternal puncture (Wright's stain), showing increased number of megakaryocytes surrounded by masses of platelets. (×70.)

Investigation of Blood-clotting Mechanism.—Clotting-time (Lee and White), 4 minutes; one-stage prothrombin time (Quick), 15 seconds (control, 15 seconds); prothrombin consumption (Biggs and McFarlane), normal; clot retraction (McFarlane), normal. Calcium clotting time of normal plasma was not increased by addition of patient's plasma. The thromboplastin generation test (Biggs and Douglas, 1953) was normal when the patient's serum was added to the control platelet suspension and the control alumina-adsorbed plasma. It was also normal when the patient's alumina-adsorbed plasma was added to the control serum and control platelet suspension and when the patient's platelet suspension, before dilution and after dilution 1 in 8, was added to the control alumina-adsorbed plasma and control serum. No defect of blood clotting could therefore be detected and the platelet factor seemed normal.

Progress and Treatment (Fig. 2)

During the six weeks from the end of October to mid-December repeated blood examinations showed a hypochromic anaemia, leucocytosis, and thrombocythaemia, the platelet count ranging from 1 to 2.5 million/c.mm. The bleeding-time was usually normal, but occasionally prolonged up to 10 minutes. Melaena continued and blood transfusions were necessary on nine occasions. Cortisone was administered for three and a half weeks in November, without any beneficial effect. On December 14, 3 millicuries of radioactive phosphorus (^{32}P) was given intravenously, the platelet count at that time being 2 million/c.mm. and leucocytes 58,000/c.mm. Two further blood transfusions were necessary during the next 10 days, and the patient was discharged from hospital at his own request on December 24. When seen a week later the haemoglobin had fallen to 6.9 g./100 ml. and a further transfusion was given.

On January 21, 1957, he was seen as an out-patient and was feeling well. No obvious bleeding from the bowel had been observed since his discharge from hospital two weeks earlier and blood examination showed: haemoglobin, 11 g./100 ml.; white cells, 7,600/c.mm.; platelets, 860,000/c.mm. By February 8 the platelet count was 340,000/c.mm. and the haemoglobin 11.5 g./100 ml. Two weeks later the platelets had risen to 910,000/c.mm. and

occult blood was again found in the stool. A further injection of 3 mC of ^{32}P was given and a course of intramuscular iron ("imferon") prescribed. Thereafter the blood picture returned to normal. Repeated testing of the stool for occult bleeding was carried out, but no further bleeding was observed and the patient regained full activity.

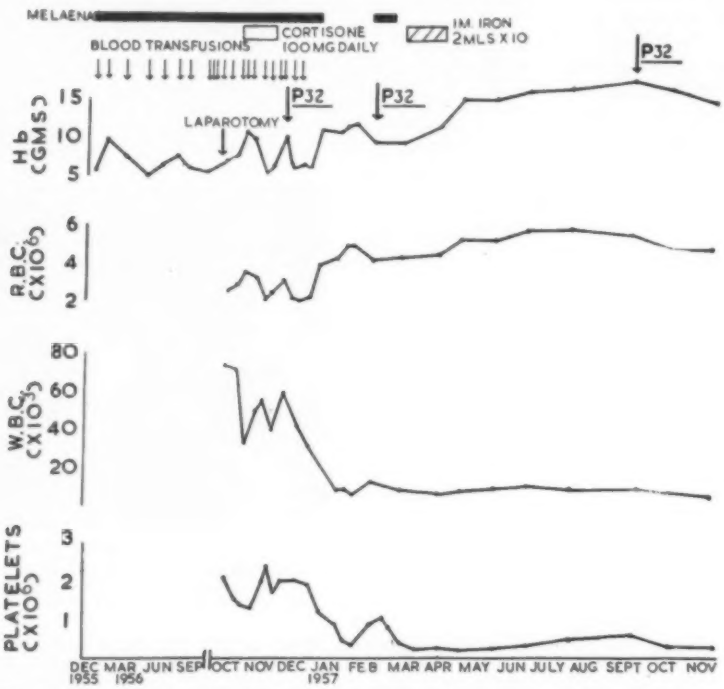

FIG. 2.—Effect of radioactive phosphorus (^{32}P) on the blood picture and bleeding tendency in Case 1.

A third injection of ^{32}P was given on September 20, when the platelet count rose to 600,000/c.mm. When last seen on November 25, 1957, the patient was symptom-free and blood examination showed: haemoglobin 14.8 g./100 ml.; red cells, 4,800,000/c.mm.; white cells, 3,800/c.mm.; platelets 320,000/c.mm.

There had been no evidence of bleeding for over nine months, whereas during the year prior to treatment with ^{32}P he had continuous melaena requiring blood transfusions at intervals of between 7 and 28 days.

Case 2

A maintenance engineer aged 53 gave a history of recurrent episodes of bleeding from the alimentary tract since 1944. Details of his case up to 1952 are deficient, but in February of that year he was admitted to Otley General Hospital under the care of Dr. R. N. Tattersall, complaining of weakness and increasing pallor. The liver was enlarged, hard, and irregular, and the spleen was palpable. Blood examination revealed an iron-deficiency anaemia (haemoglobin, 8 g./100 ml.; red cells, 4,150,000/c.mm.; white cells, 12,800/c.mm.), and the sternal marrow aspirate showed a reactive hyperplasia of the red-cell series. Portal hypertension was diagnosed. Liver-function tests were, however, normal and a barium swallow showed no evidence of oesophageal varices. Improvement in the blood picture followed a course of intravenous iron ("ferrivenin") and a satisfactory haemoglobin level was maintained thereafter until June, 1953, when a hypochromic anaemia again developed. In September, 1953, the blood findings were: haemoglobin, 5.8 g./100 ml.; red cells, 3,700,000/c.mm.; white cells, 17,400/c.mm.; platelets, 145,000/c.mm. A blood film showed marked hypochromia, anisocytosis, and microcytosis, and a polymorphonuclear leucocytosis. Blood transfusions were given, and in October a splenectomy was performed at the Otley General Hospital (Mr. D. Chamberlain).

Pathological Examination of Spleen.—It weighed 568 g. and on section had a rather "beefy" appearance. Microscopically, considerable fibrosis was evident with dilatation of sinuses, the appearances being consistent with a diagnosis of portal hypertension.

Post-operative Course

Six days after operation melaena was observed. Blood transfusions were given and blood examination a week later showed: haemoglobin, 10.1 g./100 ml.; white cells, 37,000/c.mm. (polymorphs 83%, lymphocytes 17%, nucleated red cells, 2 per 100 white cells); platelets, 1,140,000/c.mm.; bleeding-time, 7½ minutes. Melaena persisted during the following two months and repeated blood transfusions were necessary. Spontaneous improvement then occurred and the patient was discharged home on December 21. Thereafter he was seen as an out-patient at regular intervals during the succeeding three years, but melaena necessitating admission to hospital for blood transfusions still occurred. Blood examination always revealed a similar picture—namely, hypochromic anaemia, thrombocythaemia (range 880,000 to 2,100,000/c.mm.), and leucocytosis (range 20,000 to 64,000/c.mm.).

In November, 1954, he was admitted to the Leeds General Infirmary and a laparotomy was performed (Mr. G. H. Wooler) on account of recurrent melaena. Thrombosis of the splenic vein, spreading to the portal vein, was observed, and the liver was enlarged and cirrhotic. Gastric varices were ligated and the pyloric region was devascularized. A month later he developed pyloric obstruction and a gastro-enterostomy was carried out. Intermittent bleeding from the bowel, however, continued.

When first seen by me in December, 1956, the patient was anaemic and the liver was enlarged, hard, and irregular. Blood examination showed: blood group A, Rh positive; haemoglobin, 9.6 g./100 ml.; red cells, 3,500,000/c.mm.; colour index, 0.9; reticulocytes, 2%; M.C.V. 87 cubic microns; M.C.H.C., 29%; white cells, 57,600/c.mm. (neutrophils 90%, eosinophils 1%, lymphocytes 9%); platelets, 2,100,000/c.mm. The bleeding-time was five minutes and Hess's capillary resistance test was negative. A blood film revealed three nucleated red cells per 100 white cells and numerous platelets, many of which were abnormal, but no megakaryocytes. Sternal marrow aspirate showed a cellular bone marrow with normal erythropoiesis and granulocytopoiesis. Megakaryocytes were increased in number and many were observed disintegrating into masses of platelets.

Investigation of Blood-clotting Mechanism.—Clotting-time, 10 minutes; one-stage prothrombin time, 17 seconds (control, 15 seconds); clot retraction, normal. Thromboplastin generation was investigated as in Case 1 and was found to be normal when the patient's platelet suspension was mixed with control alumina-adsorbed plasma and control serum. Thromboplastin generation was not impaired when the patient's platelet suspension was diluted 1 in 8. As in Case 1, no defect in blood coagulation could be detected and the platelet factor seemed normal.

Although the possibility that the alimentary bleeding was a direct consequence of portal hypertension had to be considered, the blood picture was characteristic of haemorrhagic thrombocythaemia, and it was decided to treat him accordingly.

Progress and Treatment

He was admitted to the Leeds General Infirmary on February 15, 1957, for treatment with radioactive phosphorus. Blood examination then revealed a hypochromic anaemia: white cells, 56,000/c.mm.; platelets, 2,400,000/c.mm.; and the bleeding-time was raised to 8½ minutes. The faeces were examined daily for the presence of occult blood, and on each occasion a positive result was obtained. On February 22, 3 mC. of ^{32}P was given intravenously. A month later the platelet count had fallen to 410,000/c.mm. and bleeding had ceased. A course of intramuscular iron (imferon) was given, and on April 12 a further blood examination showed: haemoglobin, 13.8 g./100 ml.; red cells, 4,700,000/c.mm.; white cells, 18,000/c.mm.; platelets, 230,000/c.mm.

Thereafter he has been seen as an out-patient at monthly intervals. Examination of the faeces for occult bleeding has been consistently negative and the haemoglobin level normal. In June, the platelet and leucocyte counts rose and a further 3 mC. of ^{32}P was given. The red cells at this time had risen to 8,250,000/c.mm., and although the platelets and leucocytes returned to normal following treatment polycythaemia has persisted. When last seen, nine months after the start of treatment, he was symptom-free and the blood findings were: haemoglobin, 15 g./100 ml.; red cells, 8,400,000/c.mm.; white cells, 9,600/c.mm.; platelets, 265,000/c.mm.

There has been no evidence of bleeding for over eight months, whereas before treatment with ^{32}P melaena and chronic hypochromic anaemia were invariably present.

Discussion

The aetiology of thrombocythaemia and the mechanism of the associated bleeding tendency remain largely unexplained. Two factors concerning the aetiology of thrombocythaemia are, however, worthy of mention. Firstly, it is now generally recognized that the myeloproliferative disorders are closely related (Dameshek, 1951), and, whereas myeloid leukaemia and polycythaemia vera are characterized by a proliferation of myeloid and erythroid tissue respectively, excessive platelet production is the predominant feature in thrombocythaemia. The occurrence of episodes of polycythaemia in cases of thrombocythaemia, the high leucocytosis, and the presence occasionally of a small proportion of immature white cells and nucleated red cells in the peripheral blood support this concept. Similarly the occasional coexistence of haemorrhagic thrombocythaemia with myeloid leukaemia (Brugsch, 1933; Hardisty, and Wolff, 1955), myelofibrosis (Hardisty and Wolff, 1955), and polycythaemia vera (Epstein and Goedel, 1934; Uotila, 1938; Mortensen, 1948) also suggest that it is intimately connected with other proliferative disorders of the bone marrow.

The role of the spleen is a second important consideration. Hardisty and Wolff (1955) found that of 23 patients with haemorrhagic thrombocythaemia, approximately half had the spleen removed previously or the spleen was found to be atrophic. Splenectomy invariably gives rise to a temporary increase in the platelet and leucocyte counts, and on rare occasions haemorrhagic thrombocythaemia appears to follow directly on the removal of the spleen as in Case 2, in which the platelet count rose from a normal pre-operative level to 1,140,000/c.mm. within two weeks of splenectomy, accompanied by an increased bleeding-time and severe haemorrhage from the alimentary tract. The association of atrophy of the spleen with haemorrhagic thrombocythaemia was first observed by Epstein and Goedel (1934). The spleen in their case weighed only 7 g.; they considered it to be the most significant aetiological feature and concluded that the disorder was due to "splenic subfunction." Although in some instances the spleen would appear to be quite normal and in others enlarged, there seems little doubt that in a high proportion of cases of haemorrhagic thrombocythaemia the spleen, or rather its absence, is of direct aetiological significance.

Attempts have been made by several authors to divide thrombocythaemia on an aetiological basis into primary or idiopathic, and secondary types. Rarely it is primary or idiopathic, when it is not associated with any other pathological process and does not follow removal of the spleen. Case 1 appears to belong to this category. More often thrombocythaemia is secondary and follows splenectomy or is associated with splenic atrophy, polycythaemia vera, chronic myeloid leukaemia, or myelofibrosis.

The mechanism of the bleeding tendency in haemorrhagic thrombocythaemia remains unexplained. The bleeding-time in some instances is prolonged, otherwise routine investigations such as the clotting-time, clot retraction, prothrombin time, and capillary resistance are invariably normal. Hardisty and Wolff (1955) were of the opinion that the platelets were functionally abnormal, and in five patients demonstrated an abnormal thromboplastin generation test due to a qualitative deficiency of the platelets. In two of their patients the highly concentrated platelet suspensions yielded normal thromboplastin generation tests, but dilution of the suspension until it contained approximately the same number of platelets per c.mm. as the control suspensions resulted in deficient production of thromboplastin and delay in thromboplastin generation. In the remaining three patients abnormal results were obtained with both concentrated and diluted platelet suspensions. With the use of a similar technique, the thromboplastin generation tests in the two cases reported above were, however, unimpaired both before and after dilution of the patient's platelet suspension, in contrast to the findings of Hardisty and Wolff. In view of these contradictory results further studies on platelet function in thrombocythaemia are obviously indicated.

That the platelets are in some way intimately concerned with the bleeding tendency would seem to be borne out by the effect of treatment with radioactive phosphorus. In previously published papers little reference has been made to the treatment of this disorder, although Mortensen (1948), who regarded thrombocythaemia as allied to polycythaemia and leukaemia and therefore possibly amenable to radiotherapy, observed some beneficial effects of total-body irradiation. It was on similar grounds that treatment with ^{32}P was given a trial in the two cases described. The response in both instances was highly satisfactory and bleeding ceased as the platelet count returned to normal. Further injections of 3 mC. of ^{32}P were given when the platelet count again rose above normal, and on this regime both patients have continued in good health and free from bleeding episodes for nine and eight months respectively. In addition to lowering the platelet count ^{32}P also resulted in a fall of the leucocyte count to normal, and in Case 2 control of the haemorrhagic tendency was followed by a rise in the red-cell count to a polycythaemic level, which was further evidence of the close association of thrombocythaemia and other myeloproliferative disorders.

Summary

The clinical and haematological features of haemorrhagic thrombocythaemia are described and two further examples reported.

Haemorrhagic thrombocythaemia is usually associated with other myeloproliferative disorders or splenic atrophy. It may follow splenectomy but is rarely primary in that it is unassociated with other pathological processes. Case 1 belongs to the latter category, while Case 2 followed splenectomy.

The mechanism of the bleeding tendency is unknown. The bleeding-time is occasionally prolonged, but other

routine tests of haemostatic function are invariably normal. No deficiency of platelet factor as evidenced by the normal thromboplastin generation tests was detected in either of the above patients.

In both patients the platelet count returned to normal and bleeding ceased after treatment with radioactive phosphorus.

I thank Professor J. C. Goligher, Dr. R. N. Tattersall, and Mr. G. H. Wooler for permission to study patients under their care, and Dr. W. Goldie for investigation of the coagulation factors.

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CUSHING'S SYNDROME IN CHILDHOOD

REPORT OF CASE OF ADRENOCORTICAL CARCINOMA WITH EXCESSIVE ALDOSTERONE PRODUCTION

BY

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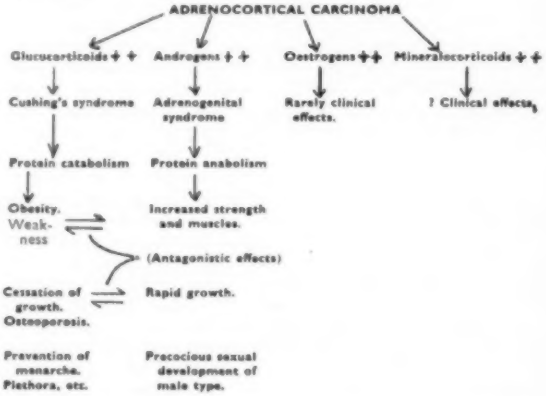
Adrenocortical overactivity in childhood may produce two distinct syndromes. The adrenogenital syndrome is caused by excessive production of androgens, and may manifest itself in three ways. If it starts in intrauterine life in a female, pseudohermaphroditism results; postnatally in a girl it produces virilism; in a boy the "pocket Hercules" variety of isosexual precocity results. An excess of glucocorticoids, on the other hand, gives rise to Cushing's syndrome, without masculinization.

Almost all cases of Cushing's syndrome in childhood are caused by adrenocortical carcinoma. Wilkins (1948) collected 70 cases of cortical carcinoma from the literature, and in his book (Wilkins, 1950) he reviewed 26 cases of Cushing's syndrome, all under the age of 10 years. Twenty-two of these were in girls; as in the adult, Cushing's syndrome in childhood is more common in females. A few other cases have been reported since then, and Guin and Gilbert (1956) produced a further review. The two cases of Cushing's syndrome not associated with carcinoma were reported by Chute *et al.* (1949) (bilateral nodular hyperplasia) and Powell *et al.* (1955) (bilateral cortical adenomas).

Functioning adenomas of the adrenal cortex at any age produce either pure Cushing's syndrome or a pure adrenogenital syndrome. Overproduction of the other two groups of adrenocortical hormones, the oestrogens and mineralocorticoids, appears to be of little importance in childhood. Oestrogen excess, leading to precocious pubertal development of female type, is extremely rare, while primary aldosteronism has not, to our knowledge, been described in childhood.

Unlike adrenal adenomas, carcinomas are biochemically pluripotent and produce excessive quantities of androgens, glucocorticoids, and also oestrogens (where these have been measured). In the case described below aldosterone was also found in great quantities in the urine. Consequently it is logical that the clinical picture may also be a mixed one in cases of carcinoma, being composed of features of Cushing's and the adrenogenital syndrome:



Since virtually all cases of Cushing's syndrome in childhood are caused by carcinoma one may expect to find evidence of the adrenogenital syndrome in all of them. On the other hand, only some adrenogenital cases (those with carcinoma) will show features of Cushing's syndrome. Now, in some ways the androgens and the glucocorticoids are mutually antagonistic, so that the resultant syndrome of excess of both may be variable. Thus androgens promote rapid skeletal growth and maturation, whereas cortisol (the chief glucocorticoid) abruptly terminates these. Androgens increase muscle bulk and power; cortisol diminishes these, producing fat from muscle and so increasing weakness. Cortisol actually opposes anabolism, leading to porosis of bone and gluconeogenesis with raising of blood sugar. Androgens tend to counteract these by promoting protein anabolism. In the case presented below the two opposing forces seemed so well titrated against each other that bone and tooth age and density, muscular configuration and power, and blood-sugar level did not appear to depart from the normal.

Case Report

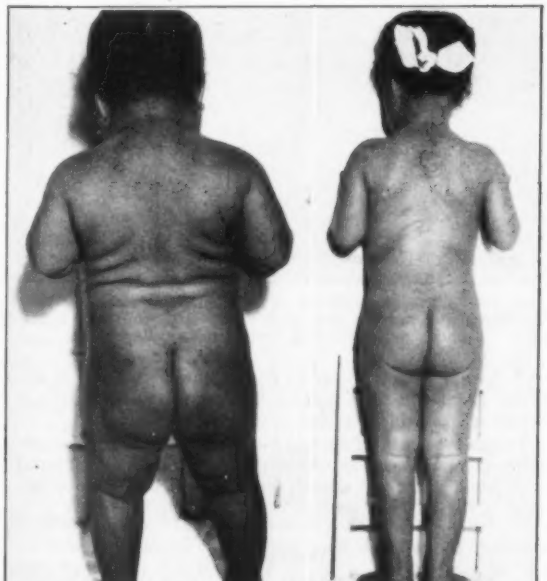
A coloured girl was admitted to Groote Schuur Hospital at the age of 2½ years. Since the age of 1 year there had been an abnormally rapid gain in weight. At this age pubic and axillary hair first appeared. Three weeks before admission a facial eruption was noticed. There was no history of menstruation.

Physical examination revealed an obese child, with a Cushing-like facies and signs of virilism (Fig. 1). The obesity included limbs as well as trunk. Her height was 31½ in. (80 cm.) and weight 39 lb. (17.7 kg.). She had a plethoric appearance and a well-marked "buffalo-neck." There was an eruption on the face, which resembled adenoma sebaceum. Axillary and pubic hair were present and the clitoris was enlarged. Strong body odour was obvious. There was no true breast development. Her B.P. was 130/90; Hb, 15 g./100 ml.; P.C.V., 45%. The specific gravity of the urine was 1015. E.C.G. was normal. Blood chemistry: serum Na,

133 mEq/l.; serum K, 5.5 mEq/l.; serum Cl, 102 mEq/l.; CO_2-combining power, 57 vols.%; blood urea, 32 mg./100 ml.; serum alkaline phosphatase, 5.3 units (Bodansky-Shinowara); serum albumin, 4.19 g./100 ml.; serum globulin, 2.89 g./100 ml.; thymol turbidity, 6.3 units; fasting blood sugar, 88 mg./100 ml.; urine concentration test, S.G. rose to 1025.

Radiographs of the long bones showed normal bone age and no osteoporosis. An intravenous pyelogram revealed normally functioning kidneys. The left kidney was depressed and a mass was visible above this kidney. Chest *x*-ray examination revealed no abnormality.

1a 1b



1c 1d

FIG. 1.—Appearance before (1a and 1c) and 12 weeks after (1b and 1d) adrenalectomy.

The 24-hour urinary output of 17-ketosteroids was 39 mg., that of 17-ketogenic steroids (Norymberski) 11.6 mg., and of aldosterone 75 μg. (expected normals for these three steroids are, respectively, under 2 mg., under 3 mg., and under 10 μg. per 24 hours).

Urinary sodium and potassium studies were made over six consecutive days. During this time basal readings were obtained and the effects of a potassium load and of prednisone administration were observed. (See section on steroids below.)

The combination of features of Cushing's syndrome and virilism at this age strongly suggested adrenocortical carcinoma, which was supported by high urinary steroid output. Pyelography indicated that the tumour was on the left side.

Course and Treatment

On March 24, 1957, 50 mg. of cortisone was given by intramuscular injection. On the morning of the 25th this was repeated, and that afternoon left-sided adrenalectomy was performed (Professor J. H. Louw), while the patient received an intravenous infusion of N/2 saline with 50 mg. of soluble cortisol (hydrocortisone). Twelve hours post-operatively the blood pressure dropped from 140/90 to 100/70. Fifty units of soluble cortisol was given intravenously and 50 mg. intramuscularly. 50 mg. of cortisone was then given intramuscularly twice daily for three days. This was replaced by oral cortisone in decreasing dosage until it was withdrawn after five days, when corticotrophin Z, 25 units, was injected intramuscularly on two occasions. Intravenous infusions were maintained for two days after operation. The subsequent post-operative course was uneventful.

Five weeks after the operation the patient had lost 3 lb. (1.4 kg.). She was no longer as plethoric as before; the facial eruption had diminished, and the body odour was less obvious. Blood pressure had dropped to 105/70. Twelve weeks after the operation her appearance had changed dramatically (Fig. 1). She had lost 4 lb. (1.8 kg.) more, her facial skin was quite clear, the buffalo-hump had disappeared, the body odour had disappeared, and the clitoris was smaller. Hirsuties was still considerable. The 24-hour urinary output of 17-ketosteroids had fallen to 1 mg.

Seven months after the operation the clitoris was of normal size and the pubic hair had almost disappeared.

Endocrine Studies

In addition to estimation of hormone output levels in basal state, the effect upon these of potassium loading and of prednisone was investigated. In primary hyperaldosteronism (due to adrenal adenoma) the aldosterone output may become demonstrably abnormal only during periods of high potassium intake (Eales and Linder, 1956). The tumour in such instances resembles the normal adrenal glomerulosa in its secretory response to hyperpotassaemia. In the present case we therefore observed the effect of an extra 100 mEq of potassium in the diet.

Secondly, the dependence of the adrenal tumour on the pituitary was studied by following the plasma cortisol and urinary steroid hormone excretion during the administration of $\triangle^1$-cortisone (prednisone) in doses of 5 mg. twice a day. Prednisone is one of the most potent suppressors of the secretion of corticotrophin by the pituitary.

Estimations of intake and urinary output of sodium and potassium were undertaken at the same time, to ascertain whether the cortical steroids were producing excessive retention of sodium or loss of potassium.

The urinary 17-ketogenic steroids and 17-ketosteroids were determined by the method of Norymberski, Stubbs, and West (1953), plasma cortisol by that of Lewis (1957), and urinary aldosterone by the physico-chemical procedure of Neher and Wettstein (1956). The ketogenic steroids are a measure of the metabolites of cortisol predominantly, but the excretory product of 17-hydroxyprogesterone also contributes to these urinary steroids. 17-Hydroxyprogesterone is andro-

genic, but is probably not secreted by the normal adrenal; it is an intermediate product in the course of the biosynthesis of glucocorticoids. Further confirmation of the nature of the substance measured by the Neher and Wettstein procedure was provided by chromatography of the acetylated urinary extract in benzene/formamide, whereby the appropriate quantity of a substance with the Rf value of aldosterone diacetate was demonstrated. The material also migrated with aldosterone in the system isoöctane/*tert*-butanol-water (Eberlein and Bongiovanni, 1955).

Results

The steroid determination (Table I) showed a striking excess of aldosterone, 17-ketosteroids, and 17-ketogenic steroids in the urine and of cortisol in the plasma, representing hypersecretion of mineralocorticoid, androgen, and glucocorticoid. Fractionation of the 17-ketosteroids showed an abnormal amount of dehydroepiandrosterone. This is the main constituent of the "β-fraction" as segregated by digitonin precipitation, and is believed to be strongly suggestive of adrenocortical carcinoma.

TABLE I

	Urinary 17-ketosteroids mg./24 Hours	Urinary 17-ketogenic Steroids mg./24 Hours	Plasma Cortisol μg./100 ml.	Urinary Aldosterone μg./24 Hours
March 3: Normal diet	39	11·6	—	—
,, 5: ,,	—	—	32	75
,, 6: Potassium load ..	48	5·8	—	—
,, 7: ,, ,,	—	—	37	75
,, 8: Prednisone ..	43	6·9	—	—
,, 9: ,, ,,	37	4·0	26	—
,, 25	Adrenalectomy			
April 7	—	—	—	10
,, 15	2·8	—	—	—
May 10	—	—	4	2
,, 11	1·0	—	—	—

Potassium loading (100 mEq in addition to normal diet) failed to augment the massive aldosterone output. Prednisone (given for only 48 hours) showed a possible suppressing effect on cortisol and 17-ketosteroid secretion on the second day, but the results were not conclusive and this suppression, if present, was not great.

Sodium and potassium "balance" data are presented in Table II. Urine collections were difficult, and were analysed only on those days when collections were virtually complete.

TABLE II.—*Electrolyte Balance*

	Sodium (mEq/24 Hours)		Potassium (mEq/24 Hours)	
	Intake	Urine	Intake	Urine
March 5: Normal diet ..	45·4	22·3	63·9	32·3
,, 6: High K intake ..	43·8	41·0	149·9	74·9
,, 8: High K intake and prednisone	47·0	36·4	157·2	78·8
,, 9: ,, ,,	45·1	33·0	152·9	81·4

We observed no evidence of any considerable retention of sodium, and certainly no excessive loss of potassium. The high potassium intake appeared to augment the urinary sodium. The prednisone had no effect on the electrolyte balance.

The gratifying clinical response to adrenalectomy was mirrored in the hormone studies, which declined to normal levels (and have remained so during a six-months follow-up).

The Adrenocortical Tumour

The specimen (Fig. 2) consisted of a triangular mass of tissue weighing 36 g. and measuring 5 cm. along each border and 3 cm. in thickness. The outer surface was smooth and encapsulated. A small breach at one point was apparently due to operative trauma. At one pole there was a projecting tag of orange-yellow tissue measuring 1.5 by 2 by 1 cm.

On cut section the greater portion was lobulated and bright orange-yellow, a smaller portion appearing more fleshy and brown.

FIG. 2.—Left adrenal gland after removal.

Sections stained with haematoxylin and eosin showed a highly anaplastic carcinoma (Fig. 3). The majority of the cells of the tumour were extremely bizarre in shape and varied considerably in size. The cytoplasm of many cells was finely granular and vacuolated. The nuclei showed many irregularities and mitotic figures were numerous. The tumour cells were divided haphazardly into groups by a fairly extensive network of thin-walled vessels. There was no haemorrhage into the tumour, and no obvious vascular infiltration was noted.

Closely applied to the tumour on its external surface was a well-marked fibrous tissue capsule. On the outer surface of this, and separated by it from the tumour, was a tag of compressed normal-looking adrenal gland tissue.

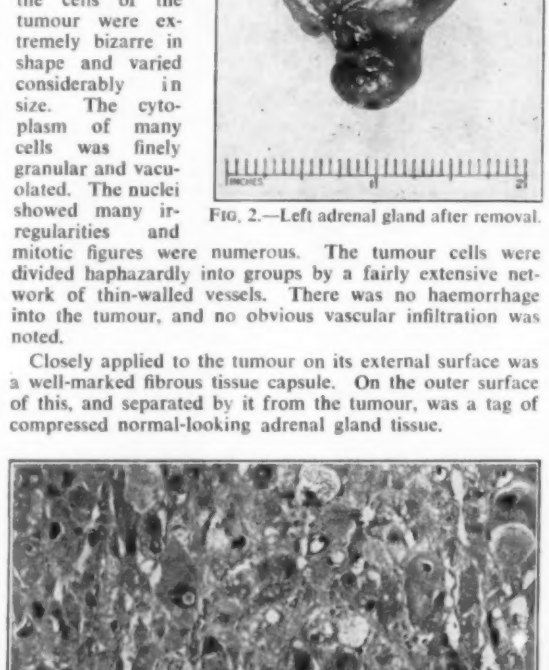


FIG. 3.—Photomicrograph of the tumour and its "capsule." (×500.) Note extreme pleomorphism of cells, and large hyperchromatic nuclei with several mitotic figures.

A frozen section showed varying amounts of fat in different areas. In some areas cells were loaded with fat; in others it was evident as fine droplets in the cytoplasm.

Ponceau–fuchsin staining of a section fixed in formol-saline showed the cytoplasm of the tumour cells to be loaded with vivid red fuchsinophil granules which were not evident in the attached portion of normal adrenal.

Discussion

Diagnosis.—In this child the clinical features of Cushing's syndrome and virilism suggested the diagnosis of adrenocortical carcinoma. The very high urinary output of 17-ketosteroids provided confirmatory evidence. An interesting

feature here was the apparent metabolic "balance" produced by the concomitant hypersecretion of glucocorticoids, mineralocorticoids and androgens. Thus there was no disturbance in muscular strength, bone growth, or electrolyte balance. The marked body odour probably was due to excessive apocrine activity. The tumour was lateralized by intravenous pyelography combined with tomography. Presacral air insufflation was rendered unnecessary by this manœuvre. It is noteworthy that the length of this history (18 months) was not incompatible with a localized carcinoma in this case.

Steroid Findings.—Despite the probable zonation of function within the normal adrenal cortex (Chute *et al.*, 1949; Landing, 1955), the tumour, a strikingly undifferentiated carcinoma, possessed the ability to synthesize all the three major groups of adrenal hormones. While the simultaneous hypersecretion of glucocorticoid and androgen by adrenal tumours is commonplace, and that of glucocorticoid and aldosterone has been described, the present case offers a remarkable example of pluripotency of an adrenal tumour. The increase in aldosterone excretion was notable not only for its magnitude but also for the absence of its expected effect on electrolyte excretion or serum potassium level. The opposing effect of androgens in promoting potassium retention may be relevant in this connexion. In common with some cases of Conn's syndrome of primary aldosteronism, sodium metabolism was not grossly disturbed; arterial hypertension was, however, present. Possible explanations for lack of electrolyte disturbances include the simultaneous hypersecretion of an unknown sodium-diuretic hormone; alternatively, some combination of known hormones may possess sodium-diuretic activity, or conceivably the renal tubular epithelium may lose its responsiveness to aldosterone.

Treatment.—When there is no evidence of secondary deposits, adrenalectomy is indicated in cases of adrenocortical carcinoma. When there is doubt about which adrenal is involved, the transperitoneal approach is favoured. Adrenalectomy may be followed by a period of hypoadrenalism, because the opposite adrenal is usually atrophic. To prevent this, cortisone is usually given pre-operatively and continued during the operation and in the immediate post-operative period. When cortisone is withdrawn, corticotrophin may be given in an effort to stimulate the remaining adrenal gland. In our patient there was a precipitous drop in the blood pressure 12 hours post-operatively. This was believed to be an indication for intravenous cortisol. It suggested that the remaining adrenal was atrophic and not also carcinomatous. The change in the appearance of the patient 12 weeks after the operation was very gratifying. A striking feature was the disappearance of the strong body odour. Though androgen overactivity as judged by the 17-ketosteroid excretion was now controlled, the hirsuties and clitoral enlargement did not disappear until a further four months had passed. These signs of virilism usually take a long time to regress and may in some instances be permanent, in which case clitoridectomy may be necessary.

Prognosis.—If the offending adrenal is removed before metastases have developed, the chances of complete cure appear to be good. Unfortunately, in many cases of Cushing's syndrome in childhood the progress is rapid and adrenalectomy useless. Our patient seems to be fortunate, and the probability of cure must be considered high, since steroid excretion has returned to a normal level.

Summary

The relationship between Cushing's syndrome in childhood and adrenocortical carcinoma is briefly considered. A "mixed picture" of Cushing's and adrenogenital syndromes is characteristic, and is illustrated by a reported case. In this patient an excessive production of glucocorticoids, androgen, and mineralocorticoids (aldosterone) was demonstrated. In some ways the usual clinical effects of each of these steroids were annulled by the opposing effects of the others.

The offending adrenocortical carcinoma was removed. Its histological appearance is described. The operation was followed by a remarkable improvement, with return to normal in the child's appearance and her hormone output.

We thank Professors J. F. Brock, G. C. Linder, F. Forman, J. H. Louw, and F. J. Ford for their continued help and interest. The patient was under the care of the latter two professors while in hospital. Dr. T. Sacks took the photomicrograph. The costs were covered by grants from the Council for Scientific and Industrial Research of South Africa and the Staff Research Fund of the University of Capetown.

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MULTIPLE EPIPHYSIAL DYSPLASIA

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Multiple epiphysial dysplasia is an uncommon condition, but is likely to be of interest to general practitioners on account of its marked familial features. Although Fairbank (1947) did not stress the genetic aspect in his original description, a number of affected families have since been recorded. Often a correct diagnosis in one member of a family will uncover several previously undiagnosed or misdiagnosed cases. Recognition of this condition is of more than academic interest, since many patients derive benefit from appropriate physiotherapy, while harm may result from treatment based on the wrong diagnosis. To make this condition more widely known, we report three further affected families, with descriptions of the clinical, radiological, and genetic features of these and previously published case reports. The family trees are shown in Figs. 1, 2, and 3. The clinical features are summarized in the Table.

Historical Note.—In 1935 Fairbank suggested the term "epiphysial dysplasia" for a patient with multiple irregular epiphysial ossification. To this title "generalisata" was added, but it was changed later to "multiplex" when the epiphysial changes were found to be multiple rather than generalized. Twelve years later he published a masterly account of the clinical and radiological features of the disease based on a study of 20 patients, many of whom had previously been reported as atypical examples of a variety of conditions, including achondroplasia, stippling of the epiphyses (dys-

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plasia epiphysialis punctata), and Morquio–Brailsford's osteochondrodystrophy. Since then a number of cases have been reported in this country—for example, three sisters by Waugh (1952); one case by Scott (1952); four cases, two of them siblings, by Watt (1952); 14 cases in three families by Maudsley (1955); three cases in three generations of one family by Shephard (1956); and, in America, six cases by Jackson *et al.* (1954)—two sporadic and four from one family—and one case by Levy *et al.* (1957).

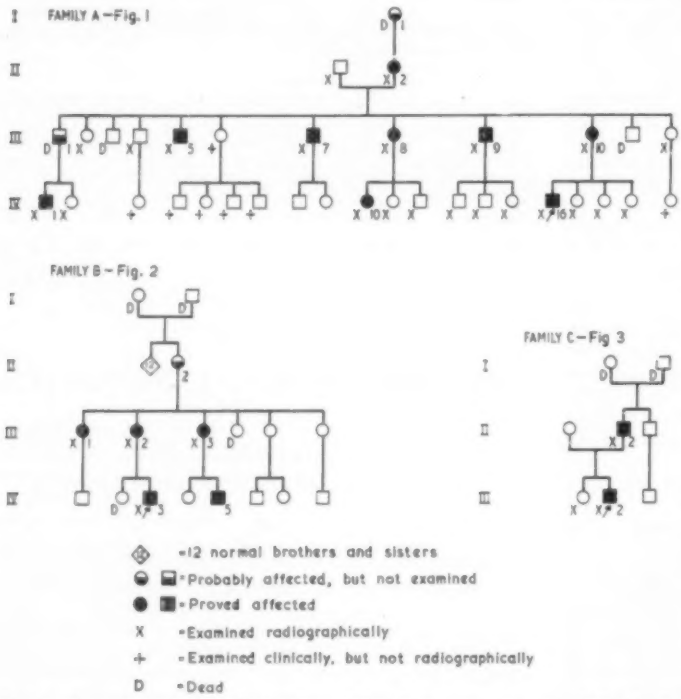

FIG. 1.—Tree of Family A. FIG. 2.—Tree of Family B. FIG. 3.—Tree of Family C.

Clinical Features

Definition.—Fairbank defined multiple epiphysial dysplasia as "a rare developmental error characterized by mottling or irregularity in density and outline of several of the developing epiphyses, dwarfism, and stubby digits."

Age at Onset.—Symptoms invariably begin in childhood, but most adults cannot recall their age at onset with any accuracy. The youngest recorded case is that of a 19-months-old infant by Gardiner-Hill (1937), while Shephard (1956) reported a probable example of the condition in an 80-year-old woman. In the present series the ages range from 2 to 71 years.

Symptoms

The most prominent symptoms are joint pain and stiffness, with a variable degree of disability. Since the lesions are multiple rather than generalized, symptoms often predominate in specific joints. Most joints have been incriminated at some time, the hips and knees being the commonest, probably because they are the most liable to weight-bearing strain. In this series the ankles, hands, and spine have also been affected, while the shoulders and elbows have caused disability in other reported cases. However, it must be emphasized that the distribution of symptomatically affected joints does not parallel the radiological distribution, which is often severest in the epiphyses of the wrists, hands, and ankles.

The degree of disability varies from slight discomfort to marked impairment of function. In family A all affected members were fully active and readily able to follow a variety of occupations, such as domestic, manual, and clerical work; none of them was able to indulge in athletic sport without after-effect, and the two youngest members often limped. In family C, in contrast, symptoms were almost continuous, and one patient could walk only with the help of a stick. With severe pain in the hip or knee,

Patients Affected with Multiple Epiphysial Dysplasia and Living in England

	Age	Sex	Symptoms: Age at Onset	Symptoms: Joints Symptomatically Affected	Symptoms: Pain	Signs: Height in cm.	Signs: Stubby Fingers	Signs: Wasting	Signs: Crepitus	Signs: Limitation of Movement	Signs: Deformity	Previous Diagnosis	Remarks
Family A:													
II 2 ..	71	F	60	Knees	+	157	+	0	−	+	0	Osteoarthritis	Some disability
III 5 ..	42	M	S.C.	Ankle, hands, knees	+	159	+	+	+	0	K.K.		" "
III 7 ..	38	M	S.C.	Knees, right hip	+	165	+	0	+	0	0		" "
III 8 ..	36	F	S.C.	Knees, ankles	+	157	0	+	+	0	K.K.		" "
III 9 ..	34	M	S.C.	Ankles, hands, knees	+	168	+	+	+	0	K.K.	Arthritis	
III 10 ..	33	F	S.C.	Knees	+	154	0	+	+	0	K.K.		Some disability
IV 1 ..	26	M	S.C.	"	+	160	+	+	+	0	"	Spinal cord lesion	
IV 10 ..	10	F	9	"	+	127	0	0	0	0	0		
IV 16 ..	9	M	3	"	+	127	+	+	+	0	K.K.		
Family B:													
III 2 ..	48	F	25	Elbow, shoulder, knees, ankles, hips, back	+	145	+	+	+	+	+	Polyarthritis	1 in. (2·5 cm.) shortening of left leg. Also wears back brace
III 3 ..	44	F	10	Hips, knees, back	+	147	+	+	+	+	+	Bilateral Perthes's disease	Severe disability necessitating cup arthroplasty
IV 3 ..	12	M	6	Hips, back	+	142	+	+	+	+	+		Waddling gait
IV 5 ..	16	M	4	Knees, hips	+	163	+	+	+	+	0	Bilateral Perthes's disease	Waddling gait; attending school for physically handicapped
Family C:													
II 2 ..	48	M	3	Ankles, hips	+	156	0	0	0	+	0	Dislocation of hip; tuberculous osteitis	Some disability
III 2 ..	4	M	1½	Nil	0	90	0	0	0	0	0	Atypical achondroplasia	Occasional limp

S.C. = Since childhood. K.K. = Knobbly knees.

patients may have great difficulty in negotiating stairs. Flexion deformities have been described, particularly of hips, knees, and elbows, while, paradoxically, hyperextensibility of joints due to laxity of the ligaments has also been reported.

Although the changes in the epiphyses are permanent, the symptoms are characteristically transient and fluctuating. Pain and stiffness are the invariable aftermath of strenuous exercise, and for this reason children and young adults are the most likely to seek medical attention. Failure to recognize the true nature of the condition may lead to a false assessment of whatever form of therapy is used, since symptoms usually subside spontaneously after a few days and may not reappear for several weeks. In later life the gradual superimposition of osteoarthritis accounts for the common complaint of pain after rest. All the affected adults of family A noticed stiffness after sitting for a few hours, and, similarly, felt worse on rising in the mornings. This has also been observed in children, and may well be a specific symptom of the disease.

Signs

Dwarfism.—Patients are characteristically short. The reduction in height is of the short-limb type, but epiphysial changes in the spine may also contribute to the shortness. Marked dwarfism is rare, but the affected members of a family can usually be singled out in being several inches shorter than unaffected members. Here comparison with relatives is more important than reference to so-called normal standards.

Stubby Digits.—This feature is probably present to some degree in all cases, and is often striking. The hand is broad, while the fingers are short, squat, and stumpy (see Fig. 4);

FIG. 4.—Broad hands; fingers short and stumpy

the nails may be deformed. The appearance is due to stunting of the phalanges and metacarpals, but gives rise to surprisingly little disability.

Enlargement of Epiphyses.—The affected epiphyses are often enlarged, and this may be accentuated by the presence of muscular wasting. Affected knees have a typical knobby appearance (see Fig. 5), which has earned one of our patients a prize in a seaside competition for knobbly knees. Epiphysial bossing may be irregular and lead to secondary deformities such as genu varum or valgum.

Limitation of Movement and Deformity.—In family A only one patient showed slight limitation of extension of the knees; family B and the father in family C, who were more severely affected, showed marked limitation of hip movement, particularly flexion and abduction. Involvement of the lower limbs leads to abnormalities of gait and posture, and a limping or waddling gait is common. Other described abnormalities include dislocation of the patellae, spinal abnormalities, platybasia, and subluxation of the elbows.

Intelligence and General Development.—The occurrence of subnormal intelligence (Fairbank, 1947), sexual infantilism (Buxton, 1930), and osteochondritis dissecans (Watt, 1952) in isolated cases is probably coincidental. No abnormalities of blood chemistry have yet been described. The association of cleft-palate in all three of Waugh's (1952) patients can hardly be coincidental; the family pattern does not fit dominant inheritance, and there was premature closure of the epiphyses, which has not been seen in other affected families, suggesting that some other condition operated in this particular family.

FIG. 5.—Knees have a knobbly appearance.

Complications

Osteoarthritis is an inevitable complication, beginning, as may be expected, in early adult life. Severe hip involvement may cause difficulty in natural childbirth and was the reason for termination of pregnancy in one member of the present series; six years later this patient underwent a cup arthroplasty for relief of marked superimposed arthritis of the hips.

Radiographic Features

Radiographic features have been well described previously, notably by Fairbank (1951). Multiple epiphysial dysplasia is a possible diagnosis in any case showing abnormal ossification of more than one epiphysis, particularly when like abnormalities can be demonstrated in other members of the family.

Typical radiographic signs are often found in the epiphyses at symptom-free joints. The changes are not necessarily generalized, and the normal appearance of many epiphyses may lead to the diagnosis not being considered. Some epiphyses may show slight irregularities of shape or ossification which assume significance only if the condition is suspected. Although the changes are usually symmetrical, there may be marked differences between the two sides, especially by the time adult life is reached. This was so in one patient (A, III 9; see Fig. 6) in whom there was gross deformity of the right femoral head; the left femoral head showed a slightly wavy outline, but the significance of this by itself might easily escape notice. Gross delay in the

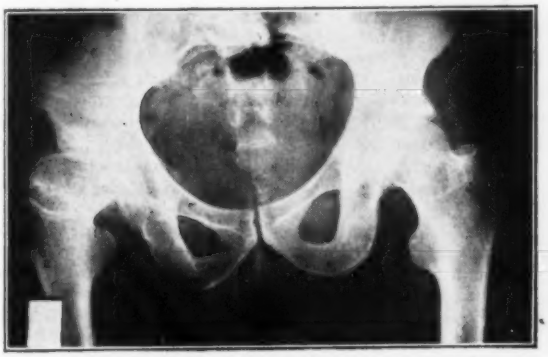

FIG. 6.—Showing deformity of right femoral head.

appearance and development of epiphyses can also occur as in the patient (C, III 2) in whom no ossification of the femoral heads could be seen at the age of 4 years (see Fig. 7): other epiphyses were thought to be normal, and the diagnosis was not made until the significance of slight thinning of the lateral part of the lower tibial epiphyses was realized. Advanced changes were then found in the hips of the child's father (see Fig. 8).

FIG. 7.—Absence of ossification of the femoral heads at the age of 4 years.

FIG. 8.—Showing advanced changes in the hips of the father of the case illustrated in Fig. 7.

Epiphyses may be seen to be arising from more than one centre of ossification. However, the appearance is quite different from that in dysplasia epiphysialis punctata, as in the condition under consideration the main bulk of the epiphyses arises from a single centre and the accessory centres are few in number and are scattered at the periphery of the cartilaginous epiphysis (see Fig. 9).

There is usually marked similarity in the radiographic features between affected members of the same family but considerable variation from one family to another. The distribution of the major changes appears to be a family characteristic. Even within families, however, some variation can occur. Moreover, members of an affected family may show such slight anomalies of epiphysial growth that it is sometimes difficult to decide, in early childhood, if they are affected or not.

Fairbank (1947) lists a number of conditions in which irregularity of the epiphyses is a feature, including cretinism, stippling of the epiphyses, osteochondrodystrophy, Perthes's disease, and dyschondroplasia. In our experience, the correct diagnosis has been neglected in favour of more common conditions. Thus in family A symptoms had been ascribed to osteoarthritis and rheumatism, two members of family B were thought to have bilateral Perthes's disease, and the father in family C had been told that he had bilateral dislocation of the hips. The radiographic appearances of multiple epiphysial dysplasia are quite distinct, however. Attention to the following points has been thought to be of most use in diagnosis :

Hands.—The carpus is small in depth and the carpal bones are irregular in shape. During childhood there is marked delay in ossification of the carpal centres, although their abnormal configuration makes accurate comparison with normal standards impossible. The central parts of the lower radial and ulnar epiphyses are thinner than normal, so that in adult life the lower ends of radius and ulna make a distinct V. The metacarpals and phalanges are not involved in all families, but are usually very short and stubby, with square angular heads.

Ankles.—There is marked thinning of the lateral part of the lower tibial epiphyses during childhood, leading in adult life to a characteristic downward inclination of the ankle-joint from the lateral to the medial side.

Knees. — The femoral and tibial condyles are square and angular. The lower end of the femur is flat and the intercondylar notch notably shallow. Irregularity of the ossification of the femoral condyles may lead to an appearance suggestive of osteochondritis dissecans.

Hips. — The femoral heads show great variation in that they may be absent, grossly deformed, irregularly ossified (as in Perthes's disease), or normal. Progressive flattening and enlargement of the femoral heads similar to that in Perthes's disease may also be seen and lead to permanent deformity and secondary osteoarthritis.

FIG. 9.—See text.

Spine.—This was not radiographed in most of our cases. One child (family B, IV 3) showed changes in the dorsal spine which, without the changes at other epiphyses, would have been indistinguishable from Scheuermann's disease. In the other affected members of this child's family the vertebral bodies appeared flat but normally ossified.

Genetic Aspects

The families were investigated by taking radiographs, so far as was possible, of the knees, ankles, and hands of all the offspring of affected individuals. It was found, however, that clinical examination was reliable for picking out those affected, and the only individuals possibly misclassified are some of the younger members of family A.

The first genetic problem is whether all cases are determined by dominant genes. Fairbank (1947) observed: "It affects both sexes, and as a rule is not inherited or familial." However, one boy appeared to have inherited from his mother, while two sisters are also included in this series. In addition he reported: "J. A. Cholmely has furnished me with details of two cases, who are brothers and apparently the only affected in a family of 10." A number of the families reported since then are similarly inconclusive from the point of genetic determination. But in 1954 Jackson *et al.* reported the disease in a mother, two sons, and a daughter, and in 1955 Maudsley reported its presence in three families. He noted that in the first of these the pattern of inheritance, with 10 of 17 members in three generations affected, strongly suggested that a dominant gene was concerned. His other two families were not fully investigated, but are compatible with determination by a dominant gene. In 1956 Shephard reported a family with three affected members in three generations, again suggesting dominant inheritance.

The three index cases in our families were unselected and were all that could be found among the children attending

the Hospital for Sick Children, Great Ormond Street. A search for further possible cases among children with the diagnostic labels "bilateral Perthes's disease" and "multiple osteochondritis" produced no cases other than one child already known to be a member of family B. In two of these families a dominant gene is clearly responsible, and the third, with father and son both affected, also suggests this type of genetic determination.

All the known examples of the condition to date, with the exception of those reported by Waugh (1952), can be ascribed to dominant inheritance. On this hypothesis, where only sibs were affected, an abnormal parent would have been found on investigation; for example, Watt (1952) notes that the parents of his patients were dead but that the father "was said to be a small man with a large body and short limbs, and had occasional trouble with his hips." On this hypothesis, also, sporadic cases will occur due to fresh mutations, as in the family with one boy affected and both parents and four sibs normal on radiographic examination (Levy *et al.*, 1957). It would appear that, while the gene may not always cause symptoms, it always leads to the development of abnormal radiographic signs.

The second genetic problem is raised by the suggestion made by Maudsley (1955) that there is a similarity of the type of affection within each family. In two of our families the affected members all showed dwarfism and major lesions in the hips, and all the adults had considerable disability. In one of these families, B, all affected members in addition had stubby hands. In family A, on the other hand, the hands were less stubby, and in some instances nearly normal, some patients were normal in height, and patients mostly complained of pain only in the knees, while several had never sought medical advice. The resemblance of the radiological features within families has already been mentioned. This suggests that two genes at least are responsible—one for the relatively mild form seen in some cases, and another for the more severe form; but to prove this point conclusively it would be necessary to take more radiographs than is justified for a point of purely theoretical importance.

Treatment

Although the pathological basis of the condition cannot be influenced in any way, it is of interest that those patients who received physiotherapy, particularly in early life, experienced considerable relief at the time and developed less disability later on. Frequent attacks of pain and stiffness are likely to cause disuse and local muscular weakness, which, in turn, favours instability of the affected joints and recurrence of further attacks of pain. Where benefit was derived from physiotherapy it could be ascribed to the measures directed to improving muscular support of the affected joints, such as non-weight-bearing exercises. One member of the second family had long remissions after courses of underwater exercises, and the children in the present series are attending regularly for non-weight-bearing exercises which they continue to practise at home, in the hope that these will prevent muscular wasting, reduce the number of acute episodes, and delay the development of osteoarthritis, which, however, will eventually dictate the form of treatment.

Illustrative Case Histories

A boy (family A, IV 16) aged 9 was referred to the Hospital for Sick Children, complaining of recurrent pain in the legs since infancy, in acute attacks at intervals of three to four months, when he would be almost completely disabled for as long as a week. Attacks were often precipitated by exercise and resolved spontaneously. His milestones were not delayed and he walked at the age of 18 months. On examination he looked thin and unwell, his height, 50 in. (127 cm.), was normal for his age, but his fingers were short, his knees knobby, and his right leg was of poor musculature (see Fig. 5). Radiographs showed the typical changes of multiple epiphysial dysplasia in him and other members of his family.

A boy (family B, IV 3) was referred to the Hospital for Sick Children at the age of 7 years with a two-year history of pain and stiffness in the left knee. On examination he had a rolling gait and slight shortening of the left leg, and it was thought that the pain in the knee was referred from the hip. Abnormality of the upper femoral epiphyses was noted on *x*-ray examination and on investigation of similar symptoms in several members of his family; the diagnosis of multiple epiphysial dysplasia was subsequently confirmed. He still has severe pain and stiffness in both hips and usually walks with a limp. On examination at the age of 12 there was some limitation of movement at both hips, his height, 56 in. (142 cm.), was below average for his age, and his fingers and toes were short and stubby. He recently developed inversion of the left foot. Skeletal survey showed dysplasia of the epiphyses of the tibiae, femora, radii, humeri, and lower dorsal spine.

A male child (family C, III 2) was referred to the Hospital for Sick Children at the age of 19 months because his parents had noticed a waddling gait, that his left leg turned out, and that he seemed short for his age. His father was said to suffer from congenital dislocation of the hips, but has since been confirmed as suffering from multiple epiphysial dysplasia. On examination the child was short—28 in. (71 cm.)—and he had a rolling gait and a lumbar lordosis with a protuberant abdomen. The main radiological abnormality was delay in the appearance of the upper femoral epiphyses, which were still not present at the age of 4 years (Fig. 7). He was otherwise well and there had been no delay in the appearance of his milestones.

Summary

Multiple epiphysial dysplasia is a genetically determined condition in which there is irregular and often retarded ossification in several of the epiphyses. Disability may be severe, with recurrent attacks of joint pain and stiffness: subsequently, osteoarthritis may lead to severe limitation of movement. The commonest sites for symptoms are the hip and knee, and the most marked signs are dwarfism and stubbiness of the fingers. The symptoms and signs are remarkably similar in the various affected members of the same family.

Three families, consisting of 15 affected members, are reported, the family pattern being that of dominant inheritance. It is suggested that dominant genes are responsible for all examples of the disorder, although more than one mutation may be concerned to account for differing degrees of severity in different families.

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Mr. RODNEY MAINGOT, F.R.C.S., was awarded a Sydney Body gold medal at a ceremony at Southend-on-Sea Hospital on May 30.

ERGOMETRINE WITH HYALURONIDASE: SPEED OF ACTION

BY

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Intravenous ergometrine given at the crowning of the foetal head or with the delivery of the anterior shoulder is a most effective means of expediting delivery of the placenta and preventing post-partum haemorrhage. This procedure was first introduced by Davis, of Chicago, in 1940. Lister (1950), in Liverpool, and Martin and Dumoulin (1953), of University College Hospital, have demonstrated its efficacy in well-planned clinical trials, and the method is now firmly established in obstetric practice.

Although the technique is widely used by obstetricians, it has one great drawback in that midwives, who in this country conduct the majority of public hospital and domiciliary deliveries, are denied its use because normally they are not trained to give intravenous injections. For this reason a simplified method is often used in which ergometrine is given by *intramuscular* injection instead of by the original intravenous route (Flew, 1947; Daley, 1951). Although some of the speed and reliability of the intravenous method is sacrificed in this modification the much greater general applicability of the intramuscular injection has led to its general acceptance.

In an attempt to enhance the value of the intramuscular method still further, Kimbell (1954) has advised that hyaluronidase ("hyalase," "rondase," "wydase") be added to the ergometrine injection. The rationale of this method is that hyaluronidase, acting as a "spreading factor," aids absorption of the drug from the injection site and so shortens the latent period inherent in all intramuscular methods. Kimbell has published results that are superior to those obtained by the plain intramuscular method and even approach the efficiency of the original intravenous technique. The merits of the ergometrine-with-hyaluronidase method justify, he believes, its routine adoption by midwives in their unsupervised practice.

Details of Investigations. The External Recording Method was used in the First Four Days of the Puerperium, the Intrauterine Balloon Method Thereafter

Case No.	Day of Puerperium	Injection Given: Ergometrine	Injection Given: Hyaluronidase	Time of Onset of Oxytocic Response	
		First Control Series			
1	8th	0·5 mg. I.M.	—	3′ 50″	
2	5th	0·5 ,, ,,	—	5′ 0″	
3	7th	0·5 ,, ,,	—	7′ 10″	
4	2nd	0·5 ,, ,,	—	7′ 10″	
5	2nd	0·5 ,, ,,	—	5′ 40″	
6	6th	0·5 ,, ,,	—	11′ 40″	Mean = 7′ 0″ (S.D. = 2′ 33″)*
7	3rd	0·5 ,, ,,	—	7′ 10″	
8	2nd	0·5 ,, ,,	—	4′ 20″	
9	5th	0·5 ,, ,,	—	7′ 10″	
10	3rd	0·5 ,, ,,	—	5′ 0″	
11	2nd	0·5 ,, ,,	—	10′ 20″	
12	3rd	0·5 ,, ,,	—	9′ 30″	
		Main Series			
13	2nd	0·5 ,, ,,	330 i.u.	4′ 0″	
14	3rd	0·5 ,, ,,	1,000 ,,	3′ 20″	
15	3rd	0·5 ,, ,,	330 ,,	5′ 30″	
16	3rd	0·5 ,, ,,	1,500 ,,	6′ 20″	
17	3rd	0·5 ,, ,,	1,500 ,,	5′ 0″	
18	3rd	0·5 ,, ,,	1,500 ,,	4′ 0″	Mean = 4′ 47″ (S.D. = 56″)*
19	2nd	0·5 ,, ,,	1,500 ,,	5′ 20″	
20	3rd	0·5 ,, ,,	1,500 ,,	5′ 20″	
21	3rd	0·5 ,, ,,	1,500 ,,	5′ 20″	
22	6th	0·5 ,, ,,	1,500 ,,	3′ 20″	
23	2nd	0·5 ,, ,,	1,500 ,,	5′ 20″	
24	2nd	0·5 ,, ,,	1,500 ,,	4′ 30″	
		Second Control Series			
25	4th	0·25 mg. I.V.	—	40″	
26	2nd	0·25 ,, ,,	—	50″	
27	2nd	0·25 ,, ,,	—	40″	Mean = 41″ (S.D. = 8″)*
28	2nd	0·5 ,, ,,	—	50″	
29	2nd	0·5 ,, ,,	—	30″	
30	2nd	0·25 ,, ,,	—	35″	

* Corrected for small series. Standard deviation = $\sqrt{\frac{\Sigma d^2}{n-1}}$

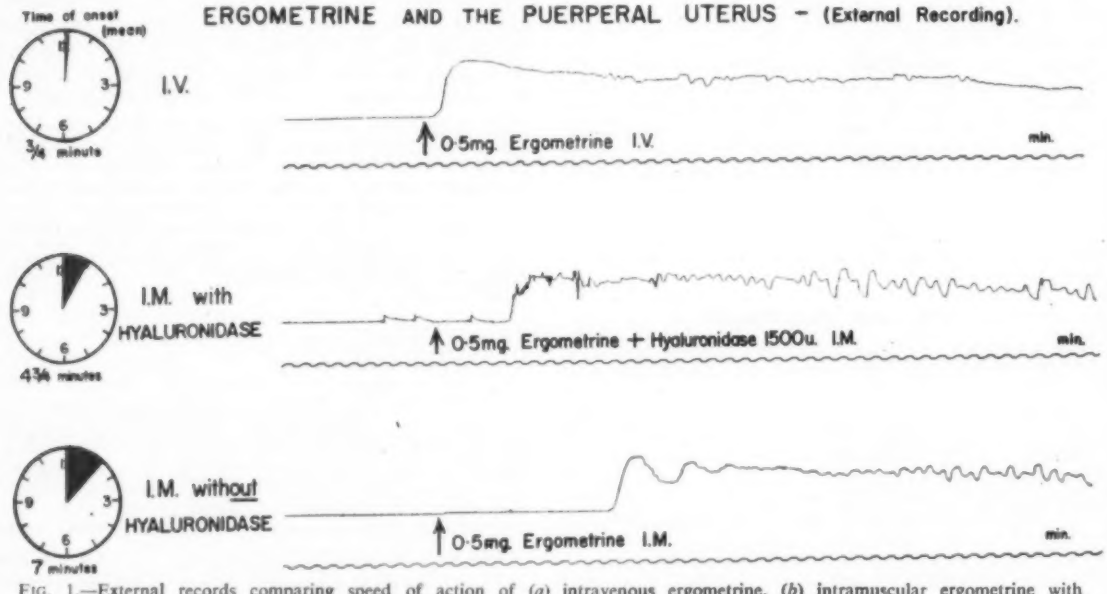

FIG. 1.—External records comparing speed of action of (*a*) intravenous ergometrine, (*b*) intramuscular ergometrine with hyaluronidase, and (*c*) intramuscular ergometrine without hyaluronidase.

This paper reports exact measurements of the delay between injection and response of (*a*) intravenous ergometrine, (*b*) intramuscular ergometrine, and (*c*) intramuscular hyaluronidase–ergometrine mixture.

Method

Records of uterine contractility were obtained from 30 healthy volunteer patients in the early days of the puerperium either, externally, by the "Oxford" tocograph (Embrey, 1955, 1958) or, internally, by the older intrauterine balloon method (Moir, 1932a, 1932b). After a suitable control period, 0.5 mg. of ergometrine maleate with added hyaluronidase was given by intramuscular injection to 12 patients (main series), and its effect on uterine contractility recorded graphically. In each case the time of onset of the oxytocic response was measured accurately for comparison with the two control groups. In one of these (first control series) 12 patients were given ergometrine *without* hyaluronidase intramuscularly; in the other (second control series) six patients received ergometrine by intravenous injection. The table shows dosage and other details.

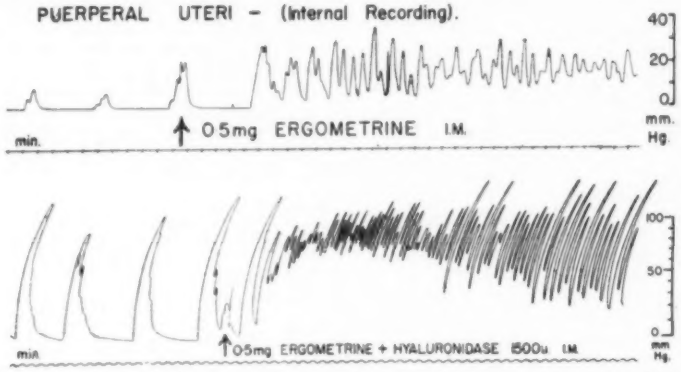

FIG. 2.—Effect of (*a*) intramuscular ergometrine and (*b*) intramuscular ergometrine with hyaluronidase as shown by internal recording.

Results

In all cases the well-known oxytocic response to ergometrine was recorded, the only difference between the various groups tested being the length of the latent period from the moment of injection to the onset of the oxytocic effect. The average times were: intravenous ergometrine, 41 seconds; intramuscular ergometrine with hyaluronidase, 4 minutes 47 seconds; and intramuscular ergometrine without hyaluronidase, 7 minutes.

Examples of records obtained with the external apparatus are shown in Fig. 1, and with the internal balloon method in Fig. 2.

Comment

The studies show that the addition of hyaluronidase to the injection undoubtedly quickens the speed of action of intramuscular ergometrine. The mean figures indicate an approximate gain of two minutes, reducing the latent period from seven minutes to five minutes. Valuable as this gain may be in a particular case, the real merit of the method has to be judged by the degree to which hyaluronidase accelerates the action of intramuscular ergometrine and approximates it to that of the intravenously injected drug. Viewed in this context, it is questionable whether a gain of two minutes is sufficient to justify the use of the ergometrine–hyaluronidase mixture routinely at the end of the second stage of labour. Again, it will be noted that even with the addition of hyaluronidase the intramuscular ergometrine still takes almost five minutes to exert its effect. This is certainly too slow for the treatment of the emergency haemorrhage. It is more than five times slower than the intravenous injection, which clearly must remain the method of choice in dealing with sudden post-partum haemorrhage. However, for the midwife who normally is not trained to make an intravenous injection, intramuscular ergometrine-with-hyaluronidase may well be worth while in such circumstances, though in practice any advantage may be annulled by the extra time required to prepare the mixed injection.

Another aspect of the matter must be considered. The present work shows that the addition of hyaluronidase confers upon the intramuscular injection of ergometrine a uniformity of action it does not otherwise possess. Without hyaluronidase the latent period before ergometrine takes effect varies considerably, and in some cases there has been a delay as long as 10 or 11 minutes (see Table). Given with hyaluronidase there is good expectation that intramuscular ergometrine will act within five minutes. The longest delay recorded with hyaluronidase in this series has been just over six minutes, which is a distinct improvement on the figures obtained when using the plain intramuscular method. It may be that in this element of uniformity lies the chief merit of the ergometrine-with-hyaluronidase injection. This could help explain the good results obtained by Kimbell in his clinical series, for the use of the hyaluronidase combination avoids the delays that may occur with the plain ergometrine.

While the addition of hyaluronidase slightly increases the speed and uniformity of action of intramuscular ergometrine, it does not follow that the plain intramuscular method is outmoded. Ergometrine alone has some advantages peculiar to itself. It is simple, more quickly prepared, quite efficacious, and better than no method at all. Finally, if midwives are to use ergometrine routinely at the end of the second stage of labour (as distinct from its use in emergency haemorrhage) supervising authorities should not lose sight of the fact that, at present, the addition of hyaluronidase to the injection quadruples the cost.

Summary

The methods of giving ergometrine by (*a*) intravenous injection, (*b*) intramuscular injection, and (*c*) intramuscular injection with added hyaluronidase at crowning of the foetal head, are reviewed and examined.

It is questionable whether the increased speed of action achieved with hyaluronidase added to the intramuscular injection of ergometrine warrants the adoption of the method routinely in the second stage of labour.

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On June 26 the DUCHESS OF DEVONSHIRE opened a new out-patient department at the Children's Hospital, Sheffield, to replace one which is now too small for its purposes. The new building, costing £110,000, has been insulated so as to lessen noise, and is provided with small "waiting areas" for the clinics instead of the usual large waiting-hall. To please the children, primary colours have been used for the decorating. The department represents the first stage in the development of the hospital.

A COMPARATIVE STUDY OF THE USE OF FERRIC CHELATE IN IRON-DEFICIENCY ANAEMIA

BY

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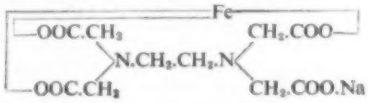
This paper presents a report on the response of iron-deficient children and young adults to three haematinics. The investigation was designed to compare established iron preparations with a recently introduced iron chelate compound in the way suggested by Cope *et al.* (1956).

Ferrous gluconate ("ferlucon") and ferrous succinate ("ferromyn") in elixir form were chosen as the established preparations. "Sytron" elixir, then on clinical trial, is a ferric sodium salt of ethylenediamine tetra-acetic acid (E.D.T.A.), and has the following structural formula :



Present Investigation

The subjects were selected from the patients in a hospital for mentally deficient children; they comprised severe mental defectives of both sexes aged 5 to 18 years. Initially, 250 patients were screened by capillary haemoglobin estimations, and those with a level below 11.5 g./100 ml. were included in the trial. Almost all of these patients were completely helpless, and had to be fed by the nursing staff: that only 30 qualified for inclusion is a tribute to the patience and devotion of the sisters and nurses.

The subjects were divided into three groups of 10 each, the groups being matched as closely as possible according to age and sex. Each group received one of the haematinics for six weeks; at the end of this period, therapy was stopped. The dose was determined according to age and the utilization factor of the haematinic used (Table I).

TABLE I.—*Doses Given*

Drug	Age in Years	Dose	Dose in mgms.	Daily Elemental Iron (mg.)	Utilization Factor	Daily Utilization (mg.)
Ferric chelate	5–10 11–18	2 dr. b.d. 2 dr. t.d.s.	600 b.d. 600 t.d.s.	142·0 213·0	Regarded as ferrous sulphate = 14%	19·9 29·8
Ferrous succinate	5–10 11–18	½ dr. t.d.s. 1 dr. b.d.	75 t.d.s. 150 b.d.	52·5 70·0	42% (Nelson, 1955)	22·4 29·4
Ferrous gluconate	5–10 11–18	1 dr. b.d. 1 dr. t.d.s.	300 b.d. 300 t.d.s.	68·0 102·0	28% (Haler, 1952)	19·0 28·5

As no utilization factor has yet been determined for ferric chelate, it was assumed to be the same as ferrous sulphate—that is, 14% (Witts, 1936).

Haemoglobin, packed cell volume, and mean corpuscular haemoglobin concentration values were determined before, at the end of, and four weeks after the trial period. Additional haemoglobin readings were taken at weekly intervals to obtain the rate of response. It was not possible to perform estimations eight weeks after the finish of the trial, because maintenance iron therapy was started before this interval had elapsed.

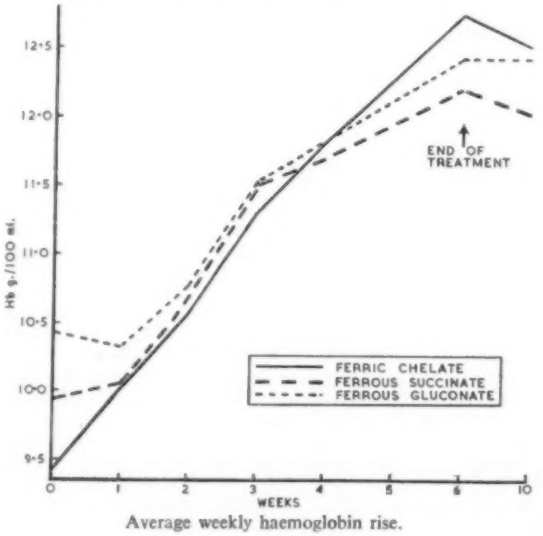
The presence of E.D.T.A. in the sytron elixir, though in small quantities, raised the question of its action upon the blood coagulation mechanisms. In order to assess the possible effect of minimal absorption of versene, prothrombin activities were carried out on this group in the middle and at the end of the trial period, and four weeks after, using the other groups as controls.

Results

Haematological Response.—Table II shows in detail the response of individual patients. It will be seen that all had a satisfactory response, as shown by a rise in the M.C.H.C. The average weekly haemoglobin rise and the total increase of haemoglobin in each patient over the period of the trial are also shown. These last values have been averaged for each group, and are shown in the Figure. From this it will be seen that the mean weekly haemoglobin rise is as follows: ferric chelate, 0.57 g./100 ml./week; ferrous succinate, 0.40 g./100 ml./week; and ferrous gluconate, 0.35 g./100 ml./week. There is a signi-

TABLE II.—*Haematological Response*

Case No.	Sex and Age	Before Trial: Hb. (g./100 ml.)	Before Trial: P.C.V. %	Before Trial: M.C.H.C. %	At End of Trial: Hb. (g./100 ml.)	At End of Trial: P.C.V. %	At End of Trial: M.C.H.C. %	Average Weekly Hb Rise (g./100 ml.)	Total Hb Rise (g./100 ml.)	Four Weeks After Trial: Hb. (g./100 ml.)	Four Weeks After Trial: P.C.V. %	Four Weeks After Trial: M.C.H.C. %
Ferric Chelate												
1	M 5	9·6	35	27	11·8	41	30	0·37	2·2	11·4	38	30
2	M 12	10·5	39	27	—	—	—	—	—	—	—	—
3	M 11	8·3	32	26	12·1	40	31	0·63	3·8	12·0	39	31
4	F 17	9·6	35	27	13·6	46	30	0·67	4·0	13·6	43	31
5	F 18	11·1	38	29	12·2	39	31	0·18	1·1	12·3	36	34
6	F 14	10·4	38	27	15·1	47	32	0·78	4·7	14·1	44	32
7	F 14	10·5	36	29	12·7	40	31	0·37	2·2	12·6	38	33
8	F 9	6·6	27	24	12·5	42	30	0·98	5·9	12·6	40	32
9	F 8	8·9	32	28	13·0	40	32	0·68	4·1	12·0	37	32
10	M 8	9·4	36	26	12·2	39	31	0·48	2·8	12·0	36	33
Ferrous Succinate												
11	M 6	10·5	37	28	12·0	38	32	0·25	1·5	11·7	35	33
12	M 9	11·2	38	29	12·6	38	33	0·23	1·4	12·0	35	34
13	M 8	10·4	37	28	12·6	38	33	0·37	2·2	12·0	37	32
14	F 18	11·7	41	28	13·6	41	33	0·31	1·9	13·6	45	31
15	F 14	10·5	36	29	12·4	38	33	0·31	1·9	12·7	41	31
16	F 11	6·6	26	25	10·6	34	32	0·67	4·0	11·1	35	32
17	F 5	9·6	33	29	12·2	37	33	0·40	2·6	11·4	32	31
18	F 12	9·3	33	28	—	—	—	—	—	—	—	—
19	F 10	9·0	32	28	10·8	32	34	0·30	1·8	10·4	29	35
20	M 16	9·4	36	26	13·4	42	32	0·67	4·0	12·7	41	31
Ferrous Gluconate												
21	M 13	10·2	36	28	12·8	42	31	0·43	2·6	12·6	41	31
22	M 16	10·5	39	27	13·2	44	30	0·45	2·7	13·0	42	31
23	M 7	11·4	41	28	13·0	43	30	0·27	1·6	11·7	39	30
24	F 5	10·5	37	28	12·3	40	31	0·30	1·8	12·5	40	31
25	F 11	8·9	32	28	10·6	34	31	0·28	1·7	11·2	34	33
26	F 18	11·2	38	29	13·2	44	30	0·33	2·0	13·6	43	32
27	F 14	9·0	35	26	12·6	43	30	0·60	3·6	12·9	42	31
28	F 8	10·9	39	28	11·4	38	30	0·08	0·5	12·1	39	31
29	F 10	10·4	37	28	12·5	41	31	0·35	2·1	12·1	40	31
30	M 9	9·4	35	27	12·1	39	31	0·45	2·7	12·0	36	33



Average weekly haemoglobin rise.

ficantly greater rise in the patients taking ferric chelate than in the other two groups ($0.05>P>0.02$). The difference between the other two groups is not significant.

Prothrombin Times.—In the group of patients taking the ferric chelate there was a prolongation of prothrombin time (as estimated by Quick's one-stage method) of 0.5 second after three weeks of treatment in three patients, and of 0.5 to 1 second after six weeks in five patients. All patients had returned to normal values four weeks after cessation of treatment. None of the patients taking ferrous succinate or gluconate showed any such alteration of prothrombin time.

Side-effects.—Diarrhoea or vomiting, or both, appeared in three patients taking ferric chelate. Cases 1 and 10 had moderate diarrhoea during the first week of the trial, but this cleared spontaneously without treatment or withdrawal of the drug. Case 2 developed severe diarrhoea and vomiting during the second week of the trial, necessitating withdrawal of the drug and vigorous rehydration therapy. Pathogens were never isolated, but in view of the severity and the timing of the attack it may be that it was not due entirely to the drug. It was not thought justifiable to reintroduce the drug after this patient's recovery. Case 28, receiving ferrous gluconate, had mild diarrhoea during the first week. Side-effects were not observed in the patients taking ferrous succinate, but in Case 18 death occurred from pneumonia during the fourth week of the trial.

Discussion

The group of patients receiving ferric chelate showed a significantly greater response to treatment than did the other two groups. They were, however, receiving very much larger quantities of elemental iron (Table I), because the utilization factor used to calculate the dose was an assumed one only. It seems likely that this assumed 14% utilization was too low, and that this accounts for the superior response. That an organic ferric salt should have such a good utilization factor is of interest, and is in marked contrast with inorganic ferric salts. It will also be noted that the dose of ferrous succinate administered was half of that normally recommended (Gillhespy, 1955), yet had as good a therapeutic effect as ferrous gluconate given in standard dosage (Hein and Keibl, 1950). The choice of iron preparation for a given patient would appear to be governed less by pharmacological considerations than by such factors as gastric tolerance, and, especially in children, palatability, together with the comparative cost of dispensing.

The slight prolongation of the prothrombin time observed in half of those taking ferric chelate is difficult to explain. Prolonged hypocalcaemia has been observed in rabbits following intravenous E.D.T.A. (Watson and Blackburn 1956), but serum calcium levels cannot be affected in man by very large oral doses of the drug (Spencer *et al.*, 1956). Although the small alteration in prothrombin time seen in this group is apparently of no clinical significance, its cause has yet to be determined.

The higher incidence of diarrhoea and vomiting in the group taking ferric chelate must also be noted. This is no isolated occurrence, since it was found in preliminary trials with the drug; large doses were taken by my colleagues and myself over several weeks, and all noted some diarrhoea. Prothrombin times were not reduced by more than the one second reported in this trial. The diarrhoea may in part be explained by the relatively large amounts of iron in the doses given, and it would seem reasonable to suggest that doses of ferric chelate lower than those used in this trial would produce an adequate haematinic response, with a reduction in side-effects.

Summary and Conclusions

A group of 30 children and young adults with iron deficiency were treated with elixirs of ferric chelate, ferrous gluconate, and ferrous succinate. Those receiving the ferric chelate showed a significantly greater response in haemoglobin rise compared with the other two groups, but this was probably due to the larger amount of utilizable iron given. Diarrhoea was more prominent, and there was some lowering of the prothrombin activity in half of this group, though not of sufficient degree to be of clinical importance. The dose of ferric chelate could probably be reduced below that given in this trial and still give an adequate haematological response but with a lessened likelihood of side-effects.

I am grateful to Dr. L. T. Hilliard, superintendent of the Fountain Hospital, Tooting, for permission to treat patients under his care, and to Professor T. Crawford and Dr. J. L. Stafford for advice and criticism. The work could not have been carried out but for the co-operation of the dispensary and nursing staff of the Fountain Hospital. The sytron was kindly supplied by Parke, Davis & Co., the ferromyn by Calmic Ltd., and the ferlucon by Evans Medical Supplies Ltd.

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TREATMENT OF ANTICHOLINESTERASE POISONING

BY

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The recent work in this Establishment (Childs *et al.*, 1955; Askew, 1956, 1957) which has been concentrated upon the search for a practical chemotherapy in organophosphate poisoning has resulted in the development of a combined treatment with 2-hydroxyiminomethyl-N-methyl pyridinium iodide (P.A.M.) and atropine. This has been shown to be effective in all the common laboratory species and against several times the LD_{50} of the more toxic organophosphates and to eliminate the necessity for artificial respiration. Recent reports from Japan (Namba and Hiraki, 1958) indicate that this treatment has now been used in organophosphate insecticide poisoning in man, in some cases with marked success.

Experiments with P2S

The latest development in these laboratories has been the use of the methane sulphonate equivalent of P.A.M., which is much more soluble than the iodide but is no less effective. We have given this the code name of P2S. Animal experiments have shown that P2S may be expected to be effective therapeutically against the common insecticides such as parathion, malathion, etc., and also against amiton when accidental poisoning has occurred in manufacture or actual use. Human tests have therefore been carried out (G. D. Wedd, H. W. Whitcher, and A. Taylor, unpublished work) in which P2S has been given by intramuscular injection of the 15% aqueous solution in doses up to 20 mg./kg. At this dosage reasonable therapeutic results have been obtained in animals. P2S has also been administered orally in capsules in doses up to 75 mg./kg. In no case have there been any deleterious effects following the administration as exemplified by clinical manifestations, by changes in E.C.G., pulse rate, or arterial blood pressure, or by alterations in the blood picture. The maximum dose of P2S so far given experimentally to one man has been 4.5 g. by mouth followed by 1 g. intramuscularly three hours later.

Further work is required before a standardized treatment can be recommended, and in any case atropine is still essential. Some of the common organophosphate insecticides, however, which themselves are relatively non-toxic to man are slowly converted in the body to very toxic substances—for example, parathion is converted into the very poisonous paraoxon. Repeated dosing with P2S and atropine may therefore be necessary to counteract the effects of successive amounts of, for example, paraoxon, as this is synthesized *in vivo* from the reservoir of parathion.

P2S tends to produce small quantities of cyanide when heated in aqueous solution, the cyanide formation being greater in neutral (*p*H 7) than in acid (*p*H 4) solution. Solid P2S decomposes when heated at 150° C. It cannot, therefore, be sterilized by heat either as the solid or in solution. However, Seitz filtration has proved satisfactory. At room temperature aqueous solutions are stable for three months provided that the *p*H is kept at 4. The solid appears to be stable indefinitely.

P2S plus atropine is unlikely to be effective against poisoning by phosphates in which a diaminoalkyl group is directly connected with the phosphorus atom as in O.M.P.A. or mipafox (Kewitz *et al.*, 1956).

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TWO CASES OF SUBCLAVIAN ANEURYSM ASSOCIATED WITH CERVICAL RIB

BY

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The vascular phenomena associated with a cervical rib, though less frequently observed than the neurological complications, are sufficiently well known that considerable discussion concerning their aetiology has arisen. Coote (1861) first described a vascular complication of a cervical rib which was treated by surgery, an aneurysm of the subclavian artery being present. The infrequency of vascular symptoms was shown in a review of 716 cases of cervical rib by Halsted (1918)—only 19 (5.3%) cases exhibited purely vascular symptoms, whilst 106 had a combination of neurological and vascular phenomena. An aneurysm was present in only 27 of the 716 cases. Eden (1939), in a review of 46 published cases, noted aneurysmal dilatation in nine, while Stammers (1950) stated that such a complication was, in his experience, very rare.

Todd (1911, 1913) postulated that the vascular changes associated with a cervical rib were trophic in nature, induced by irritation of the sympathetic fibres passing in the brachial plexus. Telford and Stopford (1931) enlarged on this theory, but suggested that irritation of the sympathetic fibres produced vasospasm, the infrequency of vascular symptoms being said to result from the distribution of the sympathetic fibres in the plexus. It was suggested that vascular phenomena developed only if there was a concentration of the sympathetic fibres in the lower trunk in its inferior part, the fibres thus being more prone to irritation than in a normal plexus. Their theory was supported by the demonstration of such an arrangement in one of nine subjects studied. The majority of evidence, however, supports the theory evolved by Lewis and Pickering (1934), who suggested that the vascular symptoms associated with a cervical rib are most probably due to local thrombosis occurring in the subclavian artery, with subsequent ejection of multiple small emboli. Such a view of the aetiology is supported by the two cases reported in this paper.

Case 1

A married woman aged 56 was admitted to hospital and was seen by me on June 17, 1949. She gave a history of sudden onset of pain in the right arm when combing her hair three months previously. The pain was followed by paraesthesia, and since that time she had had periodic attacks of pain and paraesthesia in the right arm and hand, associated with weakness of grip. She had noted some swelling at the right side of the root of the neck for the past five years.

Examination revealed a marked pallor of the distal two-thirds of all the fingers of the right hand. There was full active movement of the digits, and no muscular wasting was apparent. Immersion of the hand in warm water caused the pallor to change to a cyanotic colour. No radial pulse could be detected, but in the right side of the root of the neck a pulsatile swelling could be detected, the pulsation coinciding with the apex beat. *X*-ray examination revealed the presence of bilateral complete cervical rib. The Wassermann reaction was negative.

A diagnosis of subclavian aneurysm associated with a cervical rib was made, the peripheral vascular changes being thought to be due to multiple emboli, the pain and paraesthesia being ischaemic phenomena.

Operation.—On June 17 a right collar incision was made, the clavicular portion of the sterno-mastoid being partly divided and the brachial plexus exposed. The latter was found to be adherent to an aneurysm of the third part of the subclavian artery, the upper trunk passing anterior to the swelling. The plexus was mobilized and freed and the aneurysm resected, an abnormal vessel arising from its superior aspect being ligated prior to removal of the aneurysm. The anterior two-thirds of the cervical rib was excised and the wound closed. Section of the aneurysm revealed a thrombus adherent to its posterior and inferior walls.

On June 18 the hand was still cyanotic but the pain was relieved; normal colour was present on June 20. The patient was discharged home on June 29, when hand and shoulder movements were normal in range and power. No untoward symptoms were present on examination two months later.

When reviewed on April 13, 1955, the patient stated that she had not experienced any symptoms since the operation. There was no detectable difference in the temperature, colour, and muscle power of the upper limbs, but the right radial pulse was absent.

Case 2

A man aged 39 was admitted to hospital with a history of dull throbbing pain in the left forearm which began suddenly three months previously. The pain gradually extended up the arm and was accompanied by a feeling of coldness in the fingers. When the fingers were cold they were seen to be blue at their tips. Warmth relieved his symptoms, while cold had the opposite effect.

On examination the left hand was cold, clammy, and blue. While there was no wasting, the grip of the left hand was markedly impaired as compared with that of the right. Sensation to touch, pain, and temperature was normal. A pulsatile swelling was present in the left side of the root of the neck. The Wassermann reaction was negative. *X*-ray examination revealed the presence of a bilateral complete cervical rib.

A diagnosis of subclavian aneurysm with embolic phenomena associated with a cervical rib was made and operation advised.

Operation.—On May 19, 1954, a left collar incision was made and the brachial plexus exposed. An aneurysm of the third part of the subclavian artery was present, the upper trunk passing anterior and lateral and the middle trunk lying also anterior to the swelling, both trunks being adherent to the aneurysm. The plexus was mobilized and the aneurysm resected after division of the clavicle to remove the distal portion; the anterior two-thirds of the cervical rib was excised and the wound closed. No fixation of the clavicle was provided, the arm being retained in a sling.

On May 24 the finger movements were normal, the left hand still colder than the right, but pain had been abolished. The radial pulse was absent. Shoulder movements were begun on the fourteenth post-operative day and the patient was discharged home. When seen one month after operation there were full movements of all the joints of the left upper limb, whilst the clavicle was firmly united and the grip of the left hand was equal to that of the right. He returned to his work of dyer's operative on June 30. In February, 1955, his left hand was slightly colder and paler than the right, but function was normal and no further symptoms had been experienced.

The pathological report by Dr. I. Stewart on the sections of the aneurysm was: "The inner wall of the vessel is deformed by a flattened excrescence coated by a thin layer of laminated fibrin. Its substance is of fibrillae in which cells of the type seen in cartilage lie in pockets singly or in pairs. There are three distinct zones: in one the cells are ranged in columns with small vessels and few fibrillae; in the second and third the structure resembles cartilage but the cells differ in number. The appearances indicate repeated intravascular thrombosis with subsequent organization and cartilage deposition."

Discussion

Both cases described above exhibited purely vascular symptoms, the common initial symptoms of pallor and dull diffuse pain due to ischaemia being well demonstrated. It was thought that the release of emboli from the subclavian aneurysm accompanied by vasospasm produced the vascular symptoms, and section of both specimens reported showed intra-arterial thrombosis. It is evident, however, that there was also a vasospastic element in the development of their symptoms, as shown by their amelioration and improvement in the circulation of the limb after operation. It is feasible to suggest that the vasospasm is due to irritation of the sympathetic fibres in all the trunks, as these were adherent and stretched over the aneurysm. But complete recovery occurred after only a few days, indicating that the vasospastic element was merely a factor in the production of symptoms.

In treatment, excision of the rib alone or scalenotomy without any attack on the aneurysm has often been advocated. It is suggested that excision of the aneurysm is essential to eliminate further vascular symptoms. In Eden's (1939) case excision of the rib alone proved insufficient to prevent further embolic phenomena, and it is for this very reason that excision of the aneurysm should be undertaken.

Summary

Theories of aetiology of the vascular symptoms associated with cervical rib are reviewed.

Two cases of subclavian aneurysm associated with cervical rib are described.

Complete excision of the aneurysm and rib is advised to prevent recurrence of symptoms.

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SPLINTER HAEMORRHAGES

BY

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Splinter haemorrhages are recognized as a characteristic physical sign in patients with subacute bacterial endocarditis. They were first described in this condition by Horder (1920), who thought they were due either to "toxic" damage to capillary walls or to minute emboli. In their textbooks on cardiology Lewis (1942), White (1947), and Wood (1950) state that capillary fragility is increased in bacterial endocarditis and that the splinter haemorrhages and petechiae found in this condition are due to the abnormality in the capillaries. However, Bramwell and King (1942) consider that the white centres which are often seen in the petechiae in bacterial endocarditis indicate that they are embolic in origin.

McNaught (1939) and Sheldon (1941) described splinter haemorrhages seen in bacterial endocarditis in patients who had no other evidence of this disease, and this prompted us to investigate the incidence and significance of these lesions in more detail.

Present Investigation

We have examined the finger-nails of 429 patients and normal individuals and 35 cadavers. The lesions classified as splinter haemorrhages were all beneath the finger-nails; the toes were not examined. The lesions were usually brown or black in colour, but when fresh they were red, and changed in colour during the next few days; they did not blanch on pressure. They were 1 to 3 mm. long, linear, and longitudinally situated beneath the distal third of the nail. They did not fade or disappear spontaneously, but grew out with the nails and could eventually be cut off. As a rule the patient was unaware of their existence, but occasionally mild discomfort had been experienced. When the "haemorrhages" were associated with a history of recent trauma to the finger-nails they were ignored, as were blemishes which could conceivably have been due to dirt or

TABLE I.—*Incidence of Splinter Haemorrhages in Different Types of Disease*

Type of Disease	Patients with Splinter Haemorrhages		No. of Patients Without Splinter Haemorrhages
	No.	%	
Systemic arterial embolus (5 had mitral stenosis)	6	86	1
Probable bacterial endocarditis (mitral stenosis, negative blood cultures)	2	67	1
Uncomplicated mitral stenosis	10	44	13
Rheumatic fever (no evidence of mitral stenosis)	3	27	8
Proved bacterial endocarditis (mitral stenosis, positive blood culture) partially treated	1	25	3
Patients with marked purpura at time of examination	1	25	3
Arthritis other than rheumatic fever	1	20	4
Renal disease	4	20	16
Blood diseases not exhibiting purpura	6	19	25
Hypertension	3	18	14
Malignant neoplasms	4	17	19
Heart disease other than mitral stenosis	12	15	68
Miscellaneous	5	13	35
Pulmonary disease	11	12	79
Peptic ulcer	3	12	22
Nervous disease	3	11	24
Endocrine disease	2	11	17
Normal individuals	0	0	35

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ridges on the nail. Each patient was examined once only, and therefore the actual incidence of the haemorrhages is probably higher than we report.

We found splinter haemorrhages in 77 of the persons examined; in 60 cases there was more than one lesion. The highest incidence (86%) was in seven persons who had suffered recent major arterial emboli (Table I). Five of these patients had mitral stenosis, one was suffering from partially treated bacterial endocarditis, and one had had a recent coronary thrombosis. Of the other patients with mitral stenosis, 44% exhibited splinter haemorrhages, but they were no more common in those patients who were also thought to have bacterial endocarditis. However, we did not have the opportunity to examine any untreated patients with this disease, and the incidence may be higher in such individuals. Splinter haemorrhages did not occur more often in persons with auricular fibrillation than in those with sinus rhythm. In all other diseases the incidence of these lesions was about 15%.

We did not find any splinter haemorrhages in our unselected series of 35 normal persons. However, since we have been interested in this subject about a dozen acquaintances in normal health have shown us their nails, demonstrating lesions which we classify as splinter haemorrhages. We have gained the impression that they are particularly liable to occur after repeated jarring of the hand, unassociated with direct trauma to the nail. For instance, 4 out of 12 healthy young women who had played hockey during the preceding week had splinter haemorrhages under their finger-nails. The photograph shows splinter haemorrhages under the nail of an emphysematous diabetic patient with no cardiac disease who was employed in making packing-cases. Five of his finger-nails showed splinter haemorrhages, but he had no recollection of injuring his fingers recently. None of the seven persons with splinter haemorrhages who were examined after death had any demonstrable ante-mortem intracardiac thrombus. However, two had had recent major systemic arterial emboli and two had had pulmonary emboli. One of the latter had a valve-type foramen ovale, and one of the remaining three patients had gross atheroma with ulceration of the aorta. None of the 28 patients without splinter haemorrhages who were examined after death had had systemic emboli, and only two had had pulmonary emboli.

Splinter haemorrhages under the finger-nail of a man suffering from diabetes and emphysema.

We estimated the capillary fragility of 139 of our patients by means of Hess's test, performed in the following manner. A sphygmomanometer cuff was placed on the upper arm and inflated to midway between the systolic and diastolic arterial blood pressures for five minutes. A count was made of the petechiae which were produced in a circle 1 in. (2.5 cm.) in diameter drawn on the skin of the antecubital fossa. Ten or more petechiae were regarded as indicating excessive capillary fragility.

The capillary fragility was no greater in the patients who had splinter haemorrhages than in other persons (Table II). We did not find that the capillary fragility was increased in our partially treated patients with subacute bacterial endocarditis. Only one out of four grossly purpuric patients had any splinter haemorrhages.

Nail parings containing splinter haemorrhages which had grown out were treated with benzidine and barium peroxide. The lesions gave the green coloration characteristic of altered blood. Nail parings were stained with eosin and examined histologically. The splinter haemorrhages appeared to consist of a homogeneous mass of altered blood embedded in a layer of squamous cells adherent to the under surface of the cut nail.

TABLE II.—*Capillary Fragility in Patients With and Without Splinter Haemorrhages*

Type of Disease (Same Classification as in Table I)	Patients with Splinter Haemorrhages		Patients with no Splinter Haemorrhages	
	Total No. of Patients Examined	No. with more than 10 Petechiae after Hess Test	Total No. of Patients Examined	No. with more than 10 Petechiae after Hess Test
Systemic arterial embolus	3	1	0	—
Probable bacterial endocarditis	0	—	2	1
Uncomplicated mitral stenosis	7	1	5	3
Rheumatic fever	0	—	3	2
Proved bacterial endocarditis	0	—	2	1
Patients with marked purpura at time of examination	1	0	3	1
Arthritis	0	—	2	1
Renal disease	1	0	6	2
Blood diseases not exhibiting purpura	4	1	13	5
Hypertension	0	—	6	3
Heart disease other than mitral stenosis	0	—	15	4
Miscellaneous	4	0	13	2
Pulmonary disease	6	1	13	5
Peptic ulcer	2	1	4	1
Nervous disease	2	0	2	2
Endocrine disease	1	0	6	2
Normal individuals	0	—	13	2

The difference in incidence of the splinter haemorrhages in normal persons, patients with mitral stenosis, and patients with other diseases confirms our belief that the lesions are neither artifacts nor due to direct trauma to the nails. We do not think they are analogous to petechiae produced by haemorrhages from capillaries, for the following reasons. Splinter haemorrhages are linear, longitudinally placed under the nails, and do not fade as they age, characteristics which would not be expected of capillary haemorrhages. The frequency of these lesions in patients with uninfected mitral stenosis and with no signs of active rheumatic disease makes it unlikely that they are due to a toxic process acting on the capillaries, and the normal capillary fragility in these people confirms this. On the other hand, patients with mitral stenosis frequently have thrombus in the left auricle and are liable to arterial emboli. The high incidence of splinter haemorrhages in these people, and especially in those who had had recent large emboli, supports the other clinical evidence, which suggests that these lesions are embolic in origin.

However, if splinter haemorrhages are emboli in terminal digital vessels it is difficult to explain how they grow out with the nails and become embedded in the avascular squamous epithelium on the under surface of the nail. The histological appearance of splinter haemorrhages and their relation to the other tissues in the finger-tip is to be investigated further.

Summary

Examination of the finger-nails of 464 persons has shown that splinter haemorrhages occur in many patients who are not suffering from bacterial endocarditis. They occurred in 44% of patients with uninfected mitral stenosis and also in about 15% of persons with other diseases. Our evidence suggests that these lesions are usually due to emboli in the terminal vessels of the nail-bed.

We are indebted to Professor C. H. Stuart-Harris, in whose department this work was carried out, for his helpful advice and criticism. We also thank Mr. J. T. Chesterman and Dr. E. K. Blackburn for allowing us to examine their patients, and Mr. J. F. V. Larway for the photograph.

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Medical Memorandum

Perforated Duodenal Ulcer During Pregnancy

Perforation of a duodenal ulcer during pregnancy is a rare and serious condition which requires urgent treatment to obtain a successful outcome for both mother and foetus.

The following case is reported on account of the rarity and importance of the condition, and also because some interesting points occurred during treatment.

CASE REPORT

A primipara aged 30 first attended hospital for routine antenatal care at the 14th and 30th weeks of pregnancy. One week after the last attendance she was admitted with epigastric pain associated with vomiting. A tentative diagnosis of hyperemesis was made, and as the trouble rapidly subsided she was discharged after a stay of three days. She was readmitted that same evening with severe abdominal pain of 12 hours' duration. She had also vomited half a pint (284 ml.) of blood. Her previous history revealed that she had experienced indigestion for three and a half years before she became pregnant, but had never sought medical advice. For the first 30 weeks of the pregnancy she had noticed complete freedom from indigestion.

Examination revealed a young woman of slight build. She was obviously in severe pain and there was a moderate degree of shock. Her temperature was 98.4° (36.9° C.), pulse rate 140, respirations 20, and blood pressure 120/80 mm. Hg. Abdominal examination showed the uterus was 32 weeks by size and obscured most of the abdomen, but there was tenderness with guarding, mainly in the epigastrium. The foetal heart sounds were heard. There were no signs of toxaemia of pregnancy.

A tentative diagnosis of perforated duodenal ulcer was made, and in the circumstances it was decided to treat the condition conservatively by continuous gastric suction; intravenous glucose and saline solution; pethidine, 100 mg. six-hourly; injection of penicillin, 1 mega unit twice daily; and injection of streptomycin, 1 g. twice daily. For the ensuing 24 hours her general condition remained unchanged and the foetal heart sounds were still present.

The serum electrolytes were then within normal limits: Na 126 mEq/l., K 4.87 mEq/l., Cl 84 mEq/l. White blood cells, 17,000/c.mm.; haemoglobin, 84%.

However, after a further 18 hours the membranes ruptured spontaneously and after a further three hours she miscarried and delivered a stillbirth.

The abdomen was diffusely tender, with moderate rigidity, and was silent on auscultation. As her general condition was still satisfactory it was decided that laparotomy would be the safest course, and this was performed. It was by now 60 hours after the onset of pain.

Under general anaesthesia the abdomen was opened through a right upper paramedian incision. There was much odourless bile-stained fluid in the peritoneal cavity. A large perforated duodenal ulcer about 19 mm. in diameter was found on the anterior aspect of the first part of the duodenum. The edges of the perforation were clean-cut, with little surrounding oedema. The perforation was closed with five catgut sutures and the wound closed with a small suprapubic drain to the pelvis.

Gastric suction with intravenous glucose and saline solution, and antibiotics, were continued as before the operation.

Her convalescence was satisfactory, although prolonged, owing to suspicion of a formation of a subphrenic abscess, which, indeed, she never had. She was discharged from hospital two months after admission and has remained well on diet since then, with no recurrence of indigestion. A barium-meal examination performed three months after discharge showed the "duodenal cap deformed but not tender: appearances probably cicatricial."

COMMENT

During pregnancy activity of a peptic ulcer is infrequent and perforation of a peptic ulcer rare. Mussey (1927) reported only two cases of peptic ulceration in 370 operations during pregnancy at the Mayo Clinic in a period of 10 years.

In a search of the world literature Sandweiss *et al.* (1943) found 13 cases of complications of peptic ulceration during pregnancy; nine were cases of perforation and four were of haemorrhage. He found only one case of perforated duodenal ulcer in 70,310 pregnancies in Detroit in the period 1928–37, and also one case of perforated gastric ulcer in 348,310 pregnancies over a period of three years in New York. Both patients died. Avery Jones (1947) stated that no case of proved peptic ulcer was discovered among 10,000 pregnancies and 2,000 abortions that he reviewed. James (1948) reported one case of perforated duodenal ulcer at the 36th week of pregnancy in a patient with a known duodenal ulcer. Operation for suture of the perforation was performed and four days later spontaneous delivery of a living child occurred. The patient survived and six weeks afterwards a barium-meal examination showed an active duodenal ulcer.

Howkins (1950) quoted Professor Grey Turner's statement that he "has never seen undue activity of a peptic ulcer during pregnancy, but is very familiar with the opposite state of affairs where ulcer symptoms disappear during pregnancy"; also Sir Gordon Gordon-Taylor's statement that he "cannot remember a perforated gastric or duodenal ulcer during pregnancy."

Way (1945) attempted to explain the rarity of peptic ulcer and complications in pregnancy by correlating the hypochlorhydria found in these patients with the increased secretion of the anterior-pituitary-like hormones in the urine. He concluded that the greater the secretion of these latter the more marked the hypochlorhydria. This endocrine explanation appears to be the most likely reason for the rarity of peptic ulcer activity during pregnancy.

Hurst and Stewart (1929) stated that there was no doubt that pregnancy exerts a favourable influence on the symptoms of an ulcer and in some cases appears to lead to actual healing apart from any specific treatment. This they attributed to the mechanical effects of support of the stomach by the rising uterus. This is supposed to relieve the strain on the lesser curvature and improve the local circulation, which promotes healing of any ulcer.

It is noteworthy that most cases of perforated ulcers during pregnancy have a definite history or radiological proof of an ulcer prior to pregnancy. The case here reported occurred in an undiagnosed ulcer case. Treatment was at first by the conservative method, but, after miscarriage, operation revealed a large unsealed perforation, and this was closed and convalescence was uninterrupted. When the patient was seen six months later progress had been quite satisfactory.

I thank Mr. R. A. C. Owen, consultant surgeon at Walton Hospital, for his help and advice in the preparation of this paper.

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Reviews

CHRONIC SCHIZOPHRENIA

Chronic Schizophrenia. By Thomas Freeman, M.D., D.P.M., John L. Cameron, M.B., Ch.B., D.P.M., and Andrew McGhie, M.A. Preface by Anna Freud. Foreword by T. Ferguson Rodger. (Pp. 158+x. 21s.) London: Tavistock Publications, Ltd. 1958.

In this book two psychiatrists and a psychologist discuss the causation, symptomatology, and treatment of chronic schizophrenia, in part based on a study of a group of patients admitted to hospital with this illness. Dr. Anna Freud has written an appreciative preface. A psycho-analytic viewpoint on schizophrenia is put forward, and a good account is given of all the varying psycho-analytic theories about this disease that have been propounded in the last 50 years.

Of special interest is a report on the treatment of 17 chronic patients in a mental hospital, the average duration of whose illness was already eight years. A much more "permissive" regimen was used than is general in ordinary mental hospitals; other nurses in the hospital, in fact, referred to the ward used in this experiment as the rumpus room. Every encouragement was also given to nurses to try to foster as stable a personal relationship with each of their patients as possible, and this was considered by the authors to be the most important aspect of their special psycho-analytically orientated treatment. It is unfortunate that Freeman and his colleagues can as yet give no statistical details of the results achieved by the interesting regimen they devised; and this absence of figures is a weakness of much of the recent writings on the use of psycho-analytic concepts in the treatment of schizophrenia.

It is difficult, really, to compare the effects of the therapeutic methods used in this study with those that could be obtained with the skilled employment of more established methods. For instance, only one of these tragic patients had even been given the benefit of a full or modified leucotomy, though some had already spent up to 12 years of agitated misery in the back wards of the hospital concerned; only some of them seem to have had insulin, and none seems to have had the advantages of the new tranquillizing drugs in large doses. But this is a stimulating and interesting book, and certainly every method that helps even a small number of schizophrenic patients is to be welcomed. The book should be read especially by those who feel that sympathy and respect for the suffering of the individual patient need to be constantly emphasized in the psychiatric treatment of to-day.

WILLIAM SARGANT.

ANALYTICAL PSYCHOLOGY

New Developments in Analytical Psychology. By Michael Fordham, M.D., M.R.C.P., F.B.Ps.S. Foreword by C. G. Jung. (Pp. 214+xiv; illustrated. 25s.) London: Routledge and Kegan Paul. 1957.

The assembly in book form of nine papers, delivered for the most part to special audiences, is almost bound to give the effect of many targets. Yet the method has advantages for those who prefer the written to the spoken word. The appeal of this book is mainly to the psychotherapist versed in Jung's writings, but it has much to offer to the larger body of psychiatrists who make no claim to be Jungians or Freudians. Both groups will find the first essay, on "Biological Theory and the Concept of the Archetypes," worthy of their attention. It is a careful attempt to open new ground by linking the theory of the collective unconscious with accepted biological theory. The discussion centres on such themes as the possible relation between archetypes and the action of the organic nervous system; the function of the unconscious in the process of discoveries in science; the pitfalls in the attempt to make comparisons between ontological and phylogenetic development in biology or psychology.

The justification for claiming "New Developments" in the title lies, first, in the author's views on child psychology and on the analysis and ego development of children; and, secondly, in his evaluation of transference and counter-transference. In the section "Notes on the Transference," Fordham traces the expansion of Jung's teaching on the transference and adds his personal observations and opinions. Those in touch with the outlook of the C. G. Jung-Institut in Zurich may not go all the way with him, but, while stating his convictions frankly and clearly, he never slips over the border into dogmatism.

The foreword by Jung is a personal tribute to the author, special commendation being given to his presentation of the difficult subject of synchronicity as a principle of explanation, additional to causality. As Jung was the first to use the concept of synchronicity in psychology and in psychopathology his observations are of particular significance.

E. A. BENNET.

CLINICAL ENDOCRINOLOGY

Atlas of Clinical Endocrinology: Including Text of Diagnosis and Treatment. By H. Lisser, A.B., M.D., and Roberto F. Escamilla, A.B., M.D. (Pp. 476; 148 plates, 3 in colour. £7.) London: Henry Kimpton. 1957.

As is stated in a foreword, this is a clinical endocrinology for clinicians. The authors' aim is to present their large experience of clinical endocrine problems. Inclusion of the fundamentals of endocrine physiology, pathology, and chemistry was thought by the authors neither appropriate nor necessary. Emphasis is on the visual presentation, and in this volume the written word takes second place. The illustrations are excellent and most are original, with a few which are classics, such as Cushing's giant and Gilford's progeria. They are offered in profusion, and succeed in giving a vivid impression of the many visible features of the whole range of endocrine disorders. The text is brief and concise, but adequate and well up to date. Symptoms, signs, and diagnostic tests are each divided up into important, less important, and incidental—an excellent feature. The discussion is very sensible, and advice on treatment, though brief, is practical. A few relevant references are given for each section.

Many well-illustrated volumes on endocrinology have been produced, but this is very different from the majority. It contains much interesting and unusual information. There are given, for instance, good details of 30 famous giants together with the present location of skeletons of nine of these. There is an excellent table of the milestones to 2 years of life. The mode of presentation may be illustrated by the chapter on diabetes insipidus, a disorder not well suited to visual handling. Here is shown a very clear diagram of the anatomy of the supraoptic nucleus and some photomicrographs of nerve cells in a normal and a diseased supraoptic nucleus. There is an extremely vivid photograph of a man with severe diabetes insipidus, an excretory urogram showing dilatation of the urinary tract, and a cystogram of the enlarged bladder. There is a remarkable genealogical chart of a family of 679 persons, 88 of whom had the disease through seven generations. A clear chart well illustrates the difference in response of diabetes insipidus, normals, and psychogenic polydipsia in the intravenous hypertonic saline test of Carter and Robbins, and a small table compares the costs of treatment of the patients in different ways.

All other fields are handled with equal thoroughness, and the highly unusual is frequently found. There is, for instance, a page of interesting illustrations of true eunuchs from the Imperial Palace, Peking, from Zanzibar, and from Russia, showing the variety of types. Illustrations of this high quality will not date as must inevitably much of the text in any textbook. The relatively high cost of the book, inevitable in one so well produced, can be justified by the very long period of use to which such a work can be put. It will be found fascinating by all interested in endocrinology and a most valuable work of reference.

C. L. COPE.

CLINICAL ORTHOPAEDICS

Clinical Orthopaedics, No. 10. Editor-in-Chief: Anthony F. DePalma. (Pp. 367+x; illustrated. Single copy 60s., subscription copy 48s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co., Ltd. 1958.

The biographical notice in this volume of Phemister, for over 20 years professor of surgery at Chicago, is welcome, for his work on the growth of bone and on some aspects of abdominal surgery is respected in this country and he had carried out a year's research work in London. The greater part of the book is concerned with affections of epiphyses and apophyses; there is a symposium on metabolic bone disorders, and the chapters on general orthopaedics include spinal conditions and fractures around the femoral neck. As Phemister studied avascular necrosis it is fitting to find many references to this in the contribution on the epiphyses and carpal lunate. During the last 30 years much study has been made of pathological conditions of epiphyses, so that it is not surprising to find the publication of many illustrations and statistics of their origin and subsequent changes which are now familiar. The reader will welcome the chapter on treatment of avulsion of the ischial tuberosity; it includes two most striking illustrations, one being a graphic record of athletic stress on the tubers, depicting high hurdling—a pity one hurdle is falling—and the other of avulsion fracture of all four tubers in mother and daughter in an automobile accident.

Although our knowledge of general metabolism when bone changes exist is still immature, there is evidence of much research work being carried out, and the book under review includes comprehensive reports with many statistical tables, one on calcium metabolism in relation to metastatic malignancy coming from Boston, and another on the relationship of steroid hormones to the development and management of osteoporosis in ageing people from New York. Interspersed between mechanical aids for the injured femoral neck will be found a "spectator letter" on the problem of the physically handicapped children of India, where help is badly needed. Many doctors as well as most of its population are ignorant of what can be done for the deformed and injured child, and it was only 20 years ago that the first orthopaedic department was set up. The book is full of interest, and the collection of essays are of the standard found in previous volumes.

ST. J. D. BUXTON.

FANCIES IN DIET

Fat Consumption and Coronary Disease: An Evolutionary Answer to this Problem. A Basic Approach to the Prevention and Arrest of Coronary Disease. By T. L. Cleave, M.R.C.P.(Lond.). Foreword by Percy Stocks, C.M.G., M.A., M.D.(Camb.), F.R.C.P.(Lond.), F.S.S. (Pp. 40. 5s.) Bristol: John Wright and Sons Ltd. 1957.

The author's thesis is that man can rely with confidence on the instinct of appetite to tell him what he should or should not eat, but only so long as his instinct is being exercised on natural substances, not necessarily in their raw state but also cooked in a simple form. In passing, the author deplores the unnatural increase in concentrating and refining processes such as those used in commercial sugar and white flour production.

According to the author, fats existing in their natural environment, even though concentrated and isolated as in butter, can be eaten in strict proportion to appetite and are harmless. On the basis that coronary disease is commonest in the wealthy sections of the community, where least margarine is eaten, he is prepared to discount any great harm from hydrogenation. But he considers that through the agency of arbitrary meals and arbitrary food mixtures—designed or prepared by others without the consumer exercising his preference—there occurs unnatural interference with the exercise of instinct for fats. This may result in over-consumption of fat as in fried foods, pastries, batter puddings, etc. Unnatural fat consumption is likely then to give rise to a higher total fat consumption. The author considers that consumption of unnatural fat is the only causal agent of coronary disease which best fits all the facts. He considers that this disease is one of the penalties of industrialization, as are possibly many other diseases.

This essay is in essence a plea for the simpler, less sophisticated life—"A little of what you fancy does you good." It is rather a mixture of fact and considerable speculation.

D. P. CUTHBERTSON.

RHEUMATOID ARTHRITIS

La Polyarthrite Chronique Évolutive. By L. Isemein and A. M. Fournier with three collaborators. Preface by Professor F. Coste. (Pp. 315; illustrated. 3,200 frs.) Paris: Masson et Cie. 1956.

This is an exhaustive study of rheumatoid arthritis in all its aspects. It is the product of many years of fruitful collaboration between a physician and a radiologist. Although it is divided into the usual sections, these contain more than routine information, as the personal views of the writers are of considerable interest and should provoke new thought on many aspects of the multifarious problems associated with this disease. It is a useful book, more particularly for the specialist, for whom it is no doubt primarily written. It is well produced on good paper, but is deserving of a more permanent cover. It has an extensive bibliography, a few of the references being to the British literature.

W. S. C. COPEMAN.

SEX PERVERSIONS AND CRIMES

Sex Perversions and Sex Crimes. By James Melvin Reinhardt, M.A., Ph.D. (Pp. 340+x. 43s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This is an exasperating book on an important subject. Written primarily for law-enforcement officers, judges, and prosecutors, it nevertheless casts a hopeful eye on medical men and social workers. But it has four main faults. To begin with, it is written in much too journalistic a style, using such chapter headings as "Transvestism: Nature's Cruel Paradox." This is quite out of place in a scientific work, and in any case is not particularly accurate. Secondly, the author is only with difficulty able to restrain his repugnance at some of the more morbid sadistic perversions and crimes of violence. Thirdly, his case histories are not much more illuminating than those that appear in the sensational Sunday Press. The fourth objection may not be generally agreed among psychiatrists—namely, that Mr. Reinhardt's concepts of aetiology are confused and, from the psychodynamic point of view, somewhat superficial. He veers from hereditary to environmental factors, noting on the way some developmental influences of the usual familial type. But he rarely or never looks behind the conscious surface, being content to maintain that the significance behaviour has for society reacts on the behaviour—a generalization which the clinician will not find very helpful. In spite of these faults, it must be conceded that the author, who is Professor of Criminology at the University of Nebraska, has had a great deal of experience of the more regressive sexual perversions, and to those medical men who are unfamiliar with the subject the book may serve as an eye-opener. It may even put them on the *qui vive* to recognize among their adolescent patients such traits as may later take a dangerous antisocial form. This is the best that can be said of a disappointing book.

EDWARD GLOVER.

A Textbook of Histology, by A. A. Maximow and W. Bloom, has been an authoritative work on the subject for nearly 30 years. The seventh edition (W. B. Saunders Company Ltd., Philadelphia and London; 628 pages; 77s.) has been revised throughout to incorporate advances made in the last few years, and some new electron photomicrographs have been added to the many fine illustrations in the book.

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HUMAN BEHAVIOUR AND SOCIETY

"The proper study of mankind is man." This poetic dictum of Alexander Pope was the theme of Professor A. P. Thomson's presidential address at Birmingham on Monday of this week. His purpose, he said, was "to direct attention to the increasing responsibilities that society imposes upon its doctors and to examine some of the consequences that may flow from a wider range of medical activity." With this as his starting point Professor Thomson ranged far and wide in the brief but engaging compass of his talk. The doctor to-day is indeed caught up at almost every intersection of the web of human society. As a man struggling, like other men, to earn a living for himself and his family, he nevertheless enters into the lives of other workers in a way that is unique, intimate, and individual, yet with social consequences which are compelling and of growing complexity. The medical man, as Professor Thomson points out, belongs to a profession bred in a long tradition of individual freedom. It is in the conditions set by this freedom that a long line of discoveries have been made which to-day give mankind a control over his physical destiny that was scarcely dreamed of a hundred or even fifty years ago. The check imposed on bacterial infections has liberated for other purposes beds in tuberculosis sanatoria and fever hospitals. The tightening net cast over malaria is creating problems for societies in tropical countries which are almost frightening in their implications. The once comfortingly solid and seemingly indivisible atom is now, to man its discoverer, a source of unlimited power for good or evil. The medical man has to get to grips with the medical and biological problems posed by nuclear energy. Inventions and new techniques pour out thick and fast. To keep abreast with modern knowledge is a hard enough task for even the toughest-minded man with leisure into the bargain. Is it surprising, therefore, that the hard-pressed practising doctor finds it difficult to keep his head above the swirling waters of modern medical science, and feels too that all this somehow conveys a threat to his individual freedom of choice and action?

Professor Thomson, however, does not hesitate to lay down a new task for the practising doctor. There is, he says, "a clamant need for the branches of social science to make dispassionate studies of what actually happens in human societies." The medical man—especially the family doctor—has, he believes, a contribution to make in such studies. He refers to Canon Raven's suggestion "that between sociology and medicine there might well be established the same sort of unity which has been established between psychology and medicine." The family doctor is the one intimate objective witness of the stresses and strains of relationships in the fundamental unit of human society—the family. Professor Thomson therefore suggests that a team of family doctors might be linked with a university department of sociology in a joint piece of research, and proposes that some such experiment as this should be promoted jointly by the B.M.A. and the College of General Practitioners. "Adventure of this kind, a study of human behaviour in society," he finely says, "would surely restore interest in another problem of fundamental importance which we share with the whole company of thinkers, and which medicine, absorbed in the application of its new therapeutic resources, has neglected of late. What is the nature of man? How should we regard the individuals who consult us?" Here is a challenge to be taken up. Human genetics and human ecology are proper disciplines for the proper study of mankind. Modern medicine is emptying the wards of the fever hospitals and sanatoria. But the wards of the mental hospitals are full to overflowing. The study of human behaviour in society might afford at least part of the explanation of this, and of the other problems to which the new President of the B.M.A. so profitably directs the attention of his colleagues.

UNSATURATED FATS IN TREATMENT OF CORONARY DISEASE

Much has been written and spoken about dietary fats and coronary disease. An excessive intake of fat from early childhood has been incriminated by some as the cause of coronary disease, whereas others, while regarding dietary fat with suspicion, believe that there are many other aetiological facets to this disease. All would agree that coronary disease is in some way associated with a disturbance of fat metabolism, although both the aetiological and therapeutic implications of this association have yet to be determined. In experimental animals the extent and

severity of cholesterol deposition on the arterial wall and of atheromatous lesions can be directly correlated with the height and duration of hypercholesterolaemia induced by a diet high in cholesterol; moreover, reduction of hypercholesterolaemia is followed by a proportional regression of the arterial lesions. From this evidence it has been argued for the human, in whom atherosclerosis develops spontaneously by early adult life, that control of the serum cholesterol may be desirable and that reduction of hypercholesterolaemia in patients with coronary disease is beneficial. But some of the difficulties of gathering clear-cut data and of analysing them are evident from the careful study reported recently by Drs. H. Keen and G. A. Rose.[1]

Reduction of dietary cholesterol alone does not decrease the serum cholesterol significantly in man.[2] Reduction or total avoidance of dietary fat does,[3,4] but a diet sufficiently low in fat to produce lasting and significant reduction of the serum cholesterol is not tolerable to many people. Until recently, animal or saturated fats and vegetable or unsaturated fats were regarded as interchangeable so far as their effect on serum cholesterol was concerned,[5] but now evidence has accumulated that most animal fats raise the serum cholesterol and most vegetable fats lower it.[6-11] There is, however, no general agreement on the nature of the cholesterol-lowering action of unsaturated fats. From carefully controlled studies E. H. Ahrens and his colleagues[12] conclude that the more unsaturated the fat the greater the depression of serum cholesterol. On the other hand L. Horlick and B. M. Craig[13] have shown that a derivative (ethyl linoleate) of one of the unsaturated essential fatty acids, linoleic acid, lowers the serum cholesterol. L. W. Kinsell and his colleagues[14] obtained the same result with ethyl linoleate and with a derivative of another unsaturated essential fatty acid, arachidonic acid, and suggest that the cholesterol-lowering property of vegetable oils may be related more to their content of essential fatty acid than to their lack of saturation. However, the speculation that coronary disease might be due to a deficiency of essential fatty acids[15] has not been substantiated by finding a reduction in their concentration in the serum of patients with coronary disease.[16] Alternatively, corn oil, which is generally acknowledged as the most effective unsaturated vegetable oil, may have some cholesterol-lowering property not explained entirely by its fatty acid composition[17]; and J. M. R. Beveridge, W. F. Connell, and G. A. Mayer[18] think that its sterol content may partly be responsible.

Though the mechanism whereby unsaturated vegetable fats lower the plasma cholesterol is uncertain, their substitution for saturated fats is an effective dietetic treatment for the short-term reduction of serum cholesterol. This effect of unsaturated fats may, however, depend partly on simultaneous restriction of the intake of animal fats. For example, the use of safflower oil, the most unsaturated fat available to-day, as a supplement to a normal and unrestricted diet did not result in reduction of the serum cholesterol in normal subjects.[19] It has not yet been established whether reduction of the serum cholesterol can be maintained for years, though H. Malmros and G. Wigand[20] have obtained promising results during one year's substitution of corn oil for animal fats in hypercholesterolaemic patients.

What, then, is the place of unsaturated fats in the treatment of coronary disease? At present there is no evidence in man either that reduction of the serum cholesterol causes regression of atherosclerosis or that the prognosis of hypercholesterolaemic patients with coronary disease is improved by reduction of their high circulating cholesterol. Nevertheless it is probably justifiable to act on an unproved hypothesis and substitute corn oil for animal fats in the hypercholesterolaemic patient with a bad family history of coronary disease. In contrast to this experimental approach, much more basic information is required before the public can be advised either to eat less of saturated fats or more of unsaturated fats. Even so, there are already several types of milk, cheese, and margarine containing unsaturated oils available in retail stores. Some industrial firms, believing that these preparations will be commercially profitable, have launched publicity campaigns. Many people would hold, however, that some of the claims made for these foods, which can cause dyspepsia and diarrhoea and may be expensive, are unsubstantiated and premature. We are still passing through an experi-

[1] Keen, H., and Rose, G. A., *Brit. med. J.*, 1958, **1**, 1508.
[2] Keys, A., Mickelsen, O., Miller, E. V. O., Hayes, E. R., and Todd, R. L., *J. clin. Invest.*, 1950, **29**, 1347.
[3] Mellinkoff, S. M., Machella, T. E., and Reinhold, J. G., *Amer. J. med. Sci.*, 1950, **220**, 203.
[4] Kempner, W., *Amer. J. Med.*, 1948, **4**, 545.
[5] Hildreth, E. A., Mellinkoff, S. M., Blair, G. W., and Hildreth, D. M., *Circulation*, 1951, **3**, 641.
[6] Kinsell, L. W., Partridge, J., Boling, L. A., Margen, S., and Michaels, G., *J. clin. Endocr.*, 1952, **12**, 909.
[7] Kinsell, L. W., Michaels, G., Partridge, J., Boling, L. A., Balch, H. E., and Cochrane, G. C., *J. clin. Nutr.*, 1953, **1**, 224.
[8] Ahrens, E. H., Blankenhorn, D. H., and Tsaltas, T. T., *Proc. Soc. exp. Biol. (N.Y.)*, 1954, **86**, 872.
[9] Beveridge, J. M. R., Connell, W. F., Mayer, G. A., Firstbrook, J. B., and DeWolfe, M. S., *J. Nutr.*, 1955, **56**, 311.
[10] Bronte-Stewart, B., Keys, A., Brock, J. F., Moodie, A. D., Keys, M. H., and Antonis, A., *Lancet*, 1955, **2**, 1103.
[11] Malmros, H., and Wigand, G., *Minn. Med.*, 1955, **38**, 864.
[12] Ahrens, E. H., Hirsch, J., Insull, W., Tsaltas, T. T., Blomstrand, R., and Peterson, M. L., *Lancet*, 1957, **1**, 943.
[13] Horlick, L., and Craig, B. M., ibid., 1957, **2**, 566.
[14] Kinsell, L. W., Michaels, G. D., Friskey, R. W., and Splitter, S., ibid., 1958, **1**, 334.
[15] Sinclair, H. M., ibid., 1956, **1**, 381.
[16] James, A. T., Lovelock, J. E., Webb, J., and Trotter, W. R., ibid., 1957, **1**, 705.
[17] Jones, R. J., Reiss, O. K., and Huffman, S., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **93**, 88.
[18] Beveridge, J. M. R., Connell, W. F., and Mayer, G. A., *Fed. Proc.*, 1957, **16**, 11.
[19] Perkins, R., Wright, I. S., and Gatje, B. W., *J. Amer. med. Ass.*, 1958, **166**, 2132.
[20] Malmros, H., and Wigand, G., *Lancet*, 1957, **2**, 1.

mental phase in the understanding of coronary artery disease, and no specific dietary recommendations, apart from reduction of obesity, can reasonably be made.

ACCIDENT INSURANCE FOR B.M.A. MEMBERS

A new and most valuable practical benefit of membership of the B.M.A. was announced at the Representative Meeting in Birmingham last week. Full members of the British Medical Association have now the opportunity to effect a personal accident insurance on terms so highly favourable as would appear to be unobtainable anywhere else. The matter was introduced at the A.R.M. on a motion by Dr. I. M. Jones as chairman of the Private Practice Committee. The details of an unusually attractive scheme submitted by the Medical Insurance Agency were put before the Representatives and are repeated in an advertisement at pp. 7–8. The scheme provides full cover for death, loss of limbs or sight, and permanent disablement that may result from accident. Any B.M.A. member may take from one to ten units of benefit, each unit costing 10s. per annum. The maximum of ten units, then, can be taken for an annual payment of £5—of which £3 10s. is subject to tax relief within the usual statutory limitations—and for this modest outlay a cover of £10,000 is provided. As Dr. Jones explained to the R.B., the cover is world-wide in scope; there is no barrier of colour, race, or creed to acceptance in the scheme; and it is open to women doctors as well as to their male colleagues. No prior medical examination is necessary. The one essential requirement is full membership of the B.M.A. That is to say, for exactly the same premium the Australian and New Zealand member of the B.M.A. can get exactly the same cover as his fellow member in the United Kingdom.

The welcome announcement last week was the happy culmination of discussions at the last two Annual Representative Meetings. Members were becoming worried about the hazardous position of the young doctor and of those with limited years of service in the N.H.S. Last year the R.B. resolved "that Council be requested to arrange with the Medical Insurance Agency an appropriate insurance policy covering injury or loss of life incurred by doctors carrying out their practice." But the scheme now available is not restricted to accidents incurred only while at work. Any member, say, motoring abroad on holiday is as fully covered as when he is going on his rounds at home. The B.M.A. has added a novel kind of benefit for its members, and one which should go a long way to relieving an anxiety which any practising doctor must experience.

ALLERGIC GRANULOMA

About two years ago, in the United States, a new man-made dermatosis with unique features was seen, which has an important bearing on the understanding of certain problems in general pathology, and perhaps also on the pathology of berylliosis. L. F. Weber and his colleagues[1] in Chicago were the first to report cases of an unusual papular eruption of the axillae in patients who had used deodorant sticks. They were soon followed by others, and more than 70 cases have been recorded. These have now been summarized by W. B. Shelley and H. J. Hurley,[2] who have also described their researches to elucidate the pathogenesis of the disorder. Shelley gave a first-hand account of the detective trail followed when he delivered the Prosser White Oration to the St. John's Hospital Dermatological Society in London last year.[3] The clinical picture consisted of an eruption of flesh-coloured or brownish dome-shaped papules of varying sizes aggregated in the vault of the axillae. Symptoms were minimal or absent. In all cases the axillae had been shaved and a stick type of deodorant used as opposed to a liquid or cream preparation. Histologically the papules showed a sarcoidal granuloma in the dermis. No treatment had any effect on the condition, but it tended to resolve spontaneously over one or two years.

The recognition of this axillary granuloma followed very soon after the introduction of a new type of stick deodorant containing a zirconium salt. The stick was a soap-alcohol gel of sodium stearate, ethyl alcohol, carbitol, and water, to which was added about 10% of a 45% solution of sodium zirconium lactate. Zirconium is a metallic element close to titanium and hafnium in the periodic table. It has been used in medicine in various forms previously without any ill effects—for brain clips and bone screws in surgery, as an ointment for contact dermatitis, and as an intravenous solution for pyodermas. It has been administered to animals by various routes, and no adverse reactions were encountered. Hence it appeared perfectly safe to use as an anti-perspirant and deodorant in place of the standard aluminium salts.

Shelley and Hurley injected each of the constituents of the deodorant stick into control subjects. Only the sodium stearate produced a granuloma, but it occurred in every patient and resolved in a few weeks. Since the incidence of deodorant axillary granulomas was small in proportion to the large number of persons exposed, the sodium stearate could not be the cause. In an attempt to produce this condition experimentally, thirty men were asked to rub a zirconium stick into one shaved axilla and a non-zirconium stick into the other. The chances of success were not great, but one man developed the characteristic zirconium granuloma after a month, and it was confirmed by biopsy. It followed the natural history of the previously described granu-

[1] Weber, L. F., Neuhauser, I., Rubin, L., Slopyan, A. H., and Shellow, H., *J. Amer. med. Ass.*, 1956, **162**, 65.
[2] Shelley, W. B., and Hurley, H. J., *Brit. J. Derm.*, 1958, **70**, 75.
[3] —— *Trans. St. John's Hosp. Derm. Soc.*, 1957, **39**, 1.
[4] Calnan, C. D., and Sarkany, I., *Proc. roy. Soc. Med.*, 1958, **51**, 321.
[5] Wegener, F., *Verh. dtsch. path. Ges.*, 1936, **29**, 202.
[6] Zak, F. G., Strauss, L., and Churg, J., *J. invest. Derm.*, 1951, **17**, 349
[7] Sneddon, J. B., *Brit. med. J.*, 1955, **1**, 1448.
[8] —— *Postgrad. med. J.*, 1958, **34**, 262.

lomas. Intradermal injections showed that these patients were allergically sensitive to zirconium itself and reacted to minute amounts.

About thirty American deodorant products were said to contain zirconium salts at one time. It was introduced into stick deodorants in Britain in 1956, but was stopped after a period of only a few months, as soon as the possible harmful effects were brought to the notice of the manufacturers. As a result it is unlikely that the deodorant granuloma will be seen in Britain, though one patient has been reported in this country by C. D. Calnan and I. Sarkany.[4]

Allergic granulomatosis is not an entirely new concept in medicine. It has been used to designate the processes described by F. Wegener[5] and by F. G. Zak and colleagues,[6] but in neither of these has there been any clue to the identity of an allergen. The closest similarity to the zirconium granuloma is beryllium disease.[7] Apart from pulmonary lesions, patients are seen in whom a minute amount of the metal may painlessly penetrate the epidermis and give rise to a sarcoidal granuloma in the dermis. It is always associated with allergic hypersensitivity which can be demonstrated by a positive patch test. The sites of some of these positive patch tests later show a granuloma of the same type.[8] It is known that an epithelioid granuloma can be produced by many infective agents and different foreign materials. The work of Shelley and Hurley suggests the possibility that small amounts of trace metals other than beryllium and zirconium may be pathogenic as a result of hypersensitivity. They have also proved that a pure sarcoid reaction can be a manifestation of allergy.

HORMONE IN THE PINEAL GLAND

The pineal gland remains till now an unexploited organ. However, extracts of it have long been known to cause a change in skin colour when injected into frogs, toads, and fish. Whereas a hormone in the posterior lobe of the pituitary turns light-coloured frogs dark or indeed black, extracts of pineal gland have the opposite effect, and turn dark skin light. A. B. Lerner and his colleagues[1] at Yale have now isolated the active substance which has this action, and they propose to call it melatonin, though they do not say why they have chosen this name. Their original material was ox pineal gland, and they purified it by testing the effect of fractions on isolated skin of the frog *Rana pipiens* which they made dark with caffeine. Their work was done in the department of dermatology, and they used the most modern chemical methods (including counter-current distribution) such as are rarely seen used in departments of dermatology in Britain.

In preventing darkening of frog skin by the melanocyte-stimulating hormone, their new substance was found to be 100 times as active as adrenaline, 200 times as active as triiodothyronine, and 5,000 times as active as hydroxytryptamine. The new substance had no adrenaline-like activity on the rat uterus and no activity like that of hydroxytryptamine on the clam heart. It was not present in ox pituitary, or in the hypothalamus, or in any of the endocrine organs. Nor was it present in the eye. As to its chemistry, these authors confine themselves to the remark that the fluorescence and ultraviolet absorption were characteristic of hydroxyindoles.

[1] Lerner, A. B., Case, J. D., Takahashi, Y., Lee, T. H., and Mori, W., *J. Amer. chem. Soc.*, 1958, **80**, 2587.

PROTECTIVE OINTMENT AGAINST BILHARZIA

Rhodesia is developing fast. New and large irrigation projects and dams are being constructed and more farms are being opened up daily. With all these projects the risks of contracting bilharzia are increasing. It is often necessary in farming to use water from dams and streams. One source of infection is the watering of tobacco seed beds. As the water is usually pumped from the river under pressure, some of the cercariae might be killed by it, but they can withstand a pressure of 200 lb. per square inch (14 kg. per square cm.), which is higher than obtained by the ordinary farmer's pump. The infection is still more likely to occur from handling pumps suffering from mechanical breakdowns.

Dr. William Alves, director of the Bilharzia Research Laboratory in Southern Rhodesia, has therefore recently recommended the use of a repellent ointment to prevent cercarial penetration of the skin and so bilharziasis. The Commission on Schistosomiasis and Tropical Diseases of the United States Army devised this method of protecting soldiers exposed to the disease in the Far East.[1] Alves has made it clear that the ointment is not intended to protect swimmers but only those running an occupational risk. No doubt anglers may be tempted to use it, but as yet they have not been encouraged to try. The ointment is rubbed on the part of the body to be exposed to infection, such as the hands, forearms, ankles, and feet. Half an ounce (14 g.) is sufficient to cover all these parts. Alves's trials were not as extensive as those carried out by the Commission in the Philippine Islands, where a large number of compounds were incorporated into ointments applied to the shaved skin of the tails of mice. This was done in order to ascertain whether any of the ingredients protected the skin against penetration by cercariae during prolonged exposure to water. The mouse was placed in a brass cylinder with its tail exposed to water containing *Schistosoma japonicum* in a Wassermann tube so that the cercariae were more concentrated. Alves exposed his mice to water containing the cercariae of either *S. bovis* or *S. matthei*, and confirmed that the best protection was given by the following ointment, which he is now recommending:

Castor oil	40 parts
Lanolin	15 parts
Diglycol stearate	10 parts
Dibutyl phthalate	25 parts
Paraffin wax	10 parts

It is difficult to predict how efficacious this method of protection will be, but it is unlikely to be used with the constancy it might deserve. Farmers, miners, and even engineers will probably not cover their hands consistently with the ointment. Anglers may perhaps become infected through exposure of the hands to water

[1] Wright, W. H., Baumen, P. N., and Fry, N., *Amer. J. Hyg.*, 1948, **47**, 44.

harbouring cercariae, yet it is rare to see bilharzia in a person who has only fished and not swum in the water. There is unfortunately little evidence on the extent of this hazard. It is commonly assumed that cercariae can penetrate the skin of any part of the body with equal facility, but this may not be so. The skin of the hands and fingers is thicker and tougher than that of some other parts, and the cercariae may not be able to penetrate it, in which case there would be little indication for the ointment. The second variable factor in assessing the value of the ointment perhaps is that the risk of contracting the disease is greater when exposed to water at a dam or recently constructed project than to swiftly flowing water, to water at an altitude of over 6,000 ft. (1,800 m.) above sea level, or to rivers and lakes which have remained undisturbed for centuries. Men seem to be able to swim off the shores of Lake Nyasa with safety, but not in the smaller side streams entering it, on the banks of which refuse is strewn.

DISSOCIATION IN DEVELOPMENT

It is always easier to appreciate the vagaries of physical development in infancy than to recognize the aberrations of mental development, yet the latter may be of even greater importance. The outstanding "milestones," such as the age at which the head is held up and when sounds and persons are recognized, and the standard of performance with cubes and similar manipulations, are usually noted, and, since A. L. Gesell[1] and his associates brought this subject to the fore in 1925, most doctors have included some simple estimate of mental development when examining infants. With the increasing interest in such conditions as cerebral palsy and behaviour disorders in early childhood the assessment of the mental status and the likely prognosis of affected children are clearly urgent requirements, and any method of examination which will assist in providing this information is to be welcomed wholeheartedly.

Recently R. S. Illingworth[2] has drawn attention to the significance of dissociation in the different processes of growing up—as in an infant, for example, whose speech acquisition is notably in advance of, or behind, his motor development—and to the ways in which dissociation may be of diagnostic and prognostic value. He considers in particular motor development, which may be related to hypo- or hypertonia, sphincter control, development of speech, and social behaviour. As a result of his studies Illingworth concludes, for example, that isolated delay in motor development is not a sign of mental deficiency, and conversely isolated advanced motor development is not a sign of superior intelligence and may, indeed, occur in mentally defective children. Isolated delay in speech—another common and worrying problem—is likewise not a sign of mental defect and may be present in children of normal or superior intelligence. This is significantly different from delay in speech *associated with other signs of retardation,* in which the prognosis is bad. As to the age at which infants develop sphincter control, a matter equally worrying to parents, isolated delay is usually unimportant as a sign of mental development. To appreciate the signs of dissociation adds scope to the methods of assessing child health and represents an advance in technique which is well worthy of study.

[1] Gesell, A. L., *The Mental Growth of the Preschool Child*, 1925. Macmillan & Co., New York.
[2] Illingworth, R. S., *Arch. Dis. Childh.*, 1958, **33**, 118.

ADENOVIRUS VACCINE

The discovery of what are now known as adenoviruses,[1] and the realization that some of these agents are important causes of acute respiratory illnesses in military recruits[2] while others are responsible for outbreaks of acute pharyngitis and conjunctivitis in civilians,[3] gave rise to the hope that a great advance had been made towards identifying the cause of many respiratory infections of otherwise unknown aetiology which bulk so largely as a cause of human incapacity. Vaccines composed of two[4–6] or three[7] antigenic types of adenovirus inactivated by formaldehyde proved effective in preventing the acute infections by adenovirus types 3, 4, and 7, which cause much illness among newly recruited Service men in North America.

The possible value of adenovirus vaccines to civilians, and especially to children, in whom many of these infections occur, has been discussed in recent American papers by M. R. Hilleman[8] and W. S. Jordan.[9] Though the distribution of antibodies suggests that adenoviral infections are common in early life,[3 9–12] relatively few such infections have been detected in general surveys of sick persons.[11–17] In various reports reviewed by Jordan[9] evidence of adenovirus infection had been found in only 0.5 to 3% of civilian patients with various respiratory illnesses. Adenoviruses were uncommon causes of illness in a group of London families[14]; and in the U.S.A. they gave rise to only 4% of the respiratory illnesses observed in families in Cleveland[12] and not more than 10% of such illnesses seen in a group of families in Fort Leavenworth, Kansas.[19] In Great Britain, as in other countries, adenoviruses have been incriminated as the cause of outbreaks of generally brief, non-fatal

[1] Rowe, W. P., Huebner, R. J., Gilmore, L. D., Parrott, R. H., and Ward T. G., *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **84**, 570.
[2] Hilleman, M. R., and Werner, J. H., ibid., 1954, **85**, 183.
[3] Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A., *New Engl. J. Med.*, 1954, **251**, 1077.
[4] Hilleman, M. R., Stallones, R. A., Gauld, R. L., Warfield, M. S., and Anderson, S. A., *Proc. Soc. exp. Biol. (N.Y.)*, 1956, **92**, 77.
[5] —— Warfield, M. S., Anderson, S. A., and Werner, J. H., *J. Amer. med. Ass.*, 1957, **163**, 4.
[6] Stallones, R. A., Hilleman, M. R., Gauld, R. L., Warfield, M. S., and Anderson, S. A., ibid., 1957, **163**, 9.
[7] Bell, J. A., Hantover, M. J., Huebner, R. J., and Loosli, C. G., ibid., 1956, **161**, 1521.
[8] Hilleman, M. R., *Arch. intern. Med.*, 1958, **101**, 47.
[9] Jordan, W. S., ibid., 1958, **101**, 54.
[10] Hilleman, M. R., Werner, J. H., Dascomb, H. E., and Butler, R. L., *Amer. J. publ. Hlth*, 1955, **45**, 203.
[11] Balducci, D., Zaiman, E., and Tyrrell, D. A. J., *Brit. J. exp. Path.*, 1956, **37**, 205.
[12] Jordan, W. S., Badger, G. F., Curtiss, C., Dingle, J. H., Ginsberg, H. S., and Gold, E., *Amer. J. Hyg.*, 1956, **64**, 336.
[13] Evans, A. S., *New Engl. J. Med.*, 1957, **256**, 377.
[14] Andrews, B. E., McDonald, J. C., Thorburn, W. B., and Wilson, J. S., *Brit. med. J.*, 1956, **1**, 1203.
[15] Tyrrell, D. A. J., Balducci, D., and Zaiman, E., *Lancet*, 1956, **2**, 1326.
[16] Grist, N. R., Sommerville, R. G., and Carson, H. G., *Brit. med. J.*, 1957, **1**, 378.
[17] Morrison, B., Bass, D., Davis, J. A., Hobson, D., Madsen, T. I., and Masters, P. L., *Lancet*, 1957, **2**, 1077.
[18] Kendall, E. J. C., Riddle, R. W., Tuck, H. A., Rodan, K. S., Andrews, B. E., and McDonald, J. C., *Brit. med. J.*, 1957, **2**, 131.
[19] Wenner, H. A., Beran, G. W., Weston, J., and Chin, T. D. Y., *J. infect. Dis.*, 1957, **101**, 275.
[20] Pereira, H. G., and Kelly, B., *Proc. roy. Soc. Med.*, 1957, **50**, 755.
[21] Sommerville, R. G., *J. Hyg. (Lond.)*, 1958, **56**, 101.
[22] Bennett, F. M., Law, B. B., Hamilton, W., and Macdonald, A., *Lancet*, 1957, **2**, 670.
[23] Andrews, B. E., and McDonald, J. C., *Proc. roy. Soc. Med.*, 1957, **50**, 753.
[24] Jones, B. R., ibid., 1957, **50**, 758.
[25] Macfarlane, P. S., and Sommerville, R. G., *Lancet*, 1957, **1**, 770.

respiratory illness, such as febrile catarrh in the Army[13] and Air Force,[14] pharyngo-conjunctival fever in children,[14 15 18 20] and epidemic keratoconjunctivitis[21 22]; they have also been associated with sporadic infections of the respiratory tract or eyes.[11 20 23–25]

Adenovirus vaccines may prove useful for preventing outbreaks of illness in special groups such as newly recruited Service men, but on present indications it seems doubtful whether yet another series of injections would be worth while for the prevention of generally minor infections constituting only a small proportion of all the respiratory illnesses suffered by the general civilian population. Among children, however, adenovirus infections may be of greater importance, and it remains to be established whether significantly deleterious effects may result from chronic carriage of adenoviruses in lymphadenoid tissues of the body.

UNEXPLAINED MYOCARDIAL HYPERTROPHY

When the common causes of myocardial hypertrophy have been excluded there still remain a few patients whose cardiac enlargement has no apparent explanation. Asymmetrical hypertrophy of the interventricular septum or part of the wall of the left ventricle has been found in young adults, and Donald Teare[1] has recently described eight cases; three were known to have had auricular fibrillation, and there was some electrocardiographic evidence of conduction defects or myocardial damage. All but one of these eight patients collapsed and died suddenly and unexpectedly. In one family three siblings appeared to have the same condition, and two have died with unexplained asymmetrical myocardial hypertrophy. It is interesting to compare this localized hypertrophy of heart muscle with the diffuse cardiomegaly of familial type[2 3 4] and with congenital glycogenic "tumours" of the heart.[5 6] The patients with familial cardiomegaly are usually young adults, who may have heart block and may die suddenly; their hearts show a diffuse myocardial hypertrophy chiefly affecting the whole of the left ventricle. In several cases the myocardial fibres have been found to be vacuolated and contain glycogen. This raises the possibility that familial cardiomegaly may represent von Gierke's glycogen storage disease solely affecting the heart, but W. Evans[2] did not consider this to be a correct interpretation. Congenital glycogenic "tumours" of the heart are multiple myocardial nodules which are usually found in young children with tuberous sclerosis,[5 7] and the muscle fibres show vacuolated "spider" cells with demonstrable glycogen. Although these are often described as rhabdomyomata, they are believed to be of developmental origin[7 8] or to be related to a glycogen storage disturbance.[9 10]

The histological structure of asymmetrical hypertrophy appears to differ from that of familial cardiomegaly and the congenital glycogenic nodules: there is irregular overgrowth of the myocardium with bizarre arrangement of the muscle bundles, and the fibres are not vacuolated. Teare prefers to regard the asymmetrical hypertrophies as hamartomata—developmental tumour-like malformations—rather than true rhabdomyomata. It is not easy to decide if these different myocardial abnormalities are interrelated; the anatomical differences between hearts with a developmental abnormality, a metabolic defect, or a true tumour of the myocardium are not always characteristic. The families of patients with unexplained myocardial hypertrophy should be investigated. When more information is forthcoming it should be possible to decide if the localized, as well as the diffuse, forms of hypertrophy have a genetic basis.

[1] Teare, D., *Brit. Heart J.*, 1958, **20**, 1.
[2] Evans, W., ibid., 1949, **11**, 68.
[3] Campbell, M., and Turner-Warwick, M., ibid., 1956, **18**, 393.
[4] Gaunt, R. T., and Lecutier, M. A., ibid., 1956, **18**, 251.
[5] Batchelor, T. M., and Maun, M. E., *Arch. Path. (Chicago)*, 1945, **39**, 67.
[6] Landing, B. H., and Farber, S., *Tumours of Cardiovascular System*, 1956, Armed Forces Institute of Pathology, Washington.
[7] Prichard, R. W., *Arch. Path. (Chicago)*, 1951, **51**, 98.
[8] Hertzog, A. J., ibid., 1948, **47**, 191.
[9] Van Creveld, S., and van der Linde, H. M., *Arch. Dis. Childh.*, 1939, **14**, 14.
[10] Kidder, L. A., *Arch. Path. (Chicago)*, 1950, **49**, 55.

GOLD MEDAL OF THE B.M.A.

Last Monday the new President of the B.M.A., Professor A. P. Thomson, had the pleasant task of presenting the Association's Gold Medal for Distinguished Merit to Lord Adrian, O.M., F.R.S. It was awarded by the Council "in recognition of his distinguished services to medicine, particularly his research in the physiology of the nervous system." Like Sir Henry Dale, the previous recipient of the Medal, Lord Adrian has been conspicuously successful in advancing medicine by devoting his life to experiment in the laboratory. Much of the earlier work of this great physiologist was on the transmission of the nervous impulse, to the study of which he began to apply the electronic equipment, with its relatively crude thermionic valves, of the 1920's. A natural development of this interest was the study of the electric rhythms of the brain, first reported by Berger, and Lord Adrian and his colleagues were pioneers in making a rational basis for electroencephalography. Later he devoted his attention to the transmission of sensory impulses, chiefly for smell and sight. As President of the Royal Society in 1950–5 and Master of Trinity College, Cambridge, since 1951, as well as Vice-Chancellor of the University since 1957, Lord Adrian has shown his guidance outside the laboratory to be as illuminating as it was and still is within it. Another side is touched on in the citation which accompanied the presentation of the Medal: "Yet generations of medical students at Cambridge must have had a picture of you that is probably different from that conjured up by these almost overwhelming distinctions of mind and office, borne with a modesty of corresponding dimensions. It is a picture of a man bicycling from the Great Gate of Trinity to the laboratory and the lecture theatre, where the complexities of the central nervous system were made to seem even attractive by your skilful use of clinical neurology as an aid to understanding: a picture of a man for whom a host of students have felt affection as well as veneration."

Sir James Paterson Ross was re-elected President of the Royal College of Surgeons of England on July 10. Mr. A. Dickson Wright was elected, and Sir Archibald McIndoe re-elected, Vice-President.

British Medical Association

ANNUAL MEETING, BIRMINGHAM, 1958

SUMMARY OF PROCEEDINGS

THE SECTIONS

SECTION OF THORACIC MEDICINE AND SURGERY

Monday, July 14

Cortisone in Lung Disease

With the president, Mr. A. L. D'ABREU (Birmingham), in the chair, Dr. W. BROCKBANK (Manchester) described the use of cortisone in the treatment of asthma. He said that since the introduction of corticotrophin for the treatment of status asthmaticus its place had been established as a valuable remedy. The results of treatment with cortisone in chronic asthma were less definite, and the use of "blind trial" methods, with an inert control, had been necessary to assess results. Although initial improvement was good, deterioration took place after several months of treatment. Seven patients had died unexpectedly, possibly as a result of adrenal atrophy. Disturbing side-effects sometimes followed withdrawal. Accidents, operations, and infections were particular hazards at this stage. There had been an increased mortality from asthma in older patients in recent years. Steroid therapy might be partially responsible for this. Increase in weight was troublesome during treatment, but increase in blood pressure seldom occurred. Antibiotics were often helpful when infection was present. Cortisone was a habit-forming drug, even in patients deriving no benefit from its exhibition. On the whole, long-term treatment had been disappointing.

Steroid treatment was most valuable in the acute phase, not only in status asthmaticus but in patients given to spontaneous remissions. Prednisolone and cortisone were equally effective, though cortisone was preferred because it was cheaper and because complications occurred more slowly. Treatment aimed at starting with a big dose: 300 mg. of cortisone was given on the first day, the dosage reduced by 25 mg. each day, the course lasting 12 days. If patients relapsed a second course could be given safely. Other blind trials had shown that aerosol inhalations of hydrocortisone failed to bring relief, but inhalation of powdered hydrocortisone was helpful. The dose of hydrocortisone by this method was very small: presumably the drug acted by a local effect on the bronchial tree. The inhalation method was most applicable to less severe cases of asthma, but brisk systemic administration over limited periods was the treatment of choice.

Cortisone in Tuberculosis

Dr. N. W. HORNE (Edinburgh) spoke on the use of cortisone in pulmonary tuberculosis. Early work had suggested that cortisone was helpful in tuberculosis, but it was now apparent that it was not only safe but, sometimes, beneficial. In theory, cortisone was used for its pharmacological action in suppressing inflammatory tissue response. This allowed active multiplication of the tubercle bacilli, a stage at which anti-tuberculous drugs were most active. At the same time the harmful development of allergic reactions and fibrosis was suppressed. Cortisone should only be used at the same time as adequate anti-tuberculous drugs, and was often useful in suppressing hypersensitivity to these drugs. Cortisone was definitely valuable in the treatment of tuberculous pleural and pericardial effusions, the duration of the effusion being halved. It was necessary to continue the treatment for three weeks after the effusion had absorbed to prevent relapses. The value of cortisone in primary tuberculosis had not been established.

Chemotherapy was so effective in the treatment of pulmonary tuberculosis that the place of added cortisone was difficult to assess. Evidence suggested that cortisone was effective in controlling the systemic symptoms in acute cases. It was not effective in hastening sputum conversion or cavity closure. The radiological changes during cortisone treatment were more difficult to assess. Pulmonary function was probably better maintained in patients receiving cortisone. The physiological action of the drug was sometimes helpful in patients with chronic tuberculosis and impaired renal function.

Sarcoidosis

Dr. HUGH SMELLIE (London) reported on the use of cortisone in 45 patients with sarcoidosis who had been under the care of Dr. Clifford Hoyle at King's College Hospital. Cortisone was imperative in patients showing hypercalcaemia or uveitis. Four patients with hypercalcaemia and uraemia had been treated by a low-calcium diet and cortisone with excellent results. Cortisone reversed the increased calcium absorption produced by calciferol. Eleven patients with uveitis had responded swiftly, but seven had relapsed after cortisone had been withdrawn. Treatment should be continued for at least a year. The indications for treating patients with pulmonary infiltration were less definite. Thirty-nine patients had been treated and the results assessed by serial radiographs. Anti-tuberculous drugs were not used. Those treated before infiltration had been present for less than two years did best; but early treatment had to be weighed against the chance of spontaneous recovery. A defect in pulmonary diffusion capacity was an added indication for treatment. Usually the optimum time for treatment was between 18 months and 2 years from the onset. There was a liability to relapse even after a year's treatment: clearly cortisone controlled the sarcoid reaction but did not eliminate the underlying cause.

AIR COMMODORE C. A. RUMBALL (London) confined his comments to the acute form of sarcoidosis as seen in Service patients. The main clinical features of the disorder were arthralgia, erythema nodosum, fever, and sweating. Radiographs showed hilar adenopathy, the sedimentation rate was raised, and proof of the diagnosis could usually be obtained from liver biopsy or the Kveim skin reaction. At a time when cortisone was in short supply the patients had been treated by daily intravenous corticotrophin, treatment being limited to one month. Although patients with this disease showed spontaneous improvement, response to treatment was rapid, symptoms being controlled in two days. Sections from serial liver-biopsy specimens were shown to demonstrate the histological improvement.

Pulmonary Fibrosis

In describing the use of cortisone in pulmonary fibrosis Dr. A. G. W. WHITFIELD (Birmingham) showed the effect of the drug on radiation fibrosis, interstitial fibrosis (the Hamman–Rich syndrome) and collagen diseases. Radiation fibrosis, after treatment for breast carcinoma, responded well. Treatment had to be maintained for at least three months. Even in the late stages cortisone was of some value, although spontaneous improvement sometimes occurred. Anticoagulants had been used in an attempt to prevent irradiation fibrosis: cortisone had also proved an effective prophylactic. Four patients with the Hamman–Rich syndrome had been treated, but there had been no response. Of the collagen disorders, systemic lupus erythematosus responded best. In polyarthritis nodosa, pulmonary infiltration responded to cortisone. The results in scleroderma were disappointing.

Complications of Cortisone Treatment

Dr. STEPHEN GOLD (London) reviewed the indications for cortisone in dermatological practice, and analysed the complications occurring during treatment of 210 patients.

Gastro-intestinal complications included four patients who sustained perforation or haemorrhage. Glycosuria was usually transient and soon recurred when treatment stopped. Two patients had, however, succumbed to diabetic coma. Mental symptoms developed in five patients, one of whom had a previous history of psychotic disturbance. Cardiac failure developed in four patients and was associated with water retention. One patient developed active tuberculosis while on treatment. Purpura, venous thrombosis, and osteoporosis were rare complications. Complications peculiar to corticotrophin therapy were rigors when the drug was given intravenously and abscess after intramuscular injection. It was concluded that complications were rarely severe enough to merit withholding treatment.

In the discussion which followed Dr. W. S. HAYNES (Kenya) described his experiences in treating with prednisolone 40 Africans suffering from tuberculosis. He drew attention to the recurrence of fever and the appearance of a rash when the drugs were withdrawn. Dr. C. M. FLETCHER (London), Dr. K. ROBSON (London), and Dr. G. W. HEARN (Birmingham) also took part in the discussion.

SECTIONS OF OBSTETRICS AND GYNAECOLOGY AND GENERAL PRACTICE

Monday, July 14

Looking at the Cervix

Dr. H. W. DONOVAN (Birmingham), president of the Section of General Practice, took the chair at the joint meeting with the Section of Obstetrics and Gynaecology, when Professor H. C. MCLAREN (Birmingham) spoke on the use of the vaginal speculum, without examination by which he regarded no gynaecological examination as complete. In Britain the left lateral or Sims position was generally used, and one lubricated finger was passed into the vagina in order to assess the size of speculum to be inserted. In a tense, nervous patient a satisfactory examination by speculum might be impossible, in which case, if abnormality was suspected, the patient should be admitted for examination under anaesthesia. However, as Professor McLaren demonstrated by lantern slides, the interpretation of the clinical appearance of the cervix was not always easy. The cervix should be regarded as guilty until proved innocent, for now the cytological examination of smears made the diagnosis of pre-invasive cancer possible. General practitioners should therefore be encouraged to screen normal patients by cervical smears at regular intervals, sending the slides to a special centre for reading. If 10,000 fit women were examined in this way there would be discovered 60 women with pre-cancer of the cervix, 20 with early cancer of the cervix, and 10 with cancer of the body of the uterus.

In the subsequent discussion Professor ALEC AGNEW (Vancouver) said that cytological screening was the greatest recent advance in the diagnosis of gynaecological cancer, and described how in his area the general practitioners played the main part in carrying out these examinations. Dr. E. VON KUENSSBERG (Edinburgh) added that in Edinburgh, under the aegis of the College of General Practitioners, family doctors had carried out such a campaign with very encouraging results, especially in the diagnosis of pre-invasive cancer in women under 40 years of age.

Episiotomy

Mr. J. D. S. FLEW (London) read a paper on episiotomy and methods of perineal repair. He said that the indications for episiotomy were to forestall a spontaneous tear; for ease of vaginal manipulations—e.g., in forceps delivery; for all breech and all premature deliveries; to give more room when the subpubic angle was narrow; to help shorten the second stage in the interests of mother or baby; and as a long-term policy to prevent future prolapse. Except when undertaken immediately preceding vaginal manipulations, episiotomy was performed when the presenting part was well on the perineum, so that the consequent relief of tension would result in immediate delivery. In cases of foetal distress with the head on the perineum, episiotomy would lead to a quicker delivery than would forceps. In forceps extraction the instrument could usually be applied and the head brought down on to the perineum before performing the perineal incision. The anatomy of the area made a median episiotomy ideal, but to prevent extension into the rectum a J-shaped incision was preferred; but in every case the incision must start in the midline at the fourchette and extend throughout the depth of tissue and not merely cut the skin.

If episiotomy were urgent it could be done at the height of a pain with no anaesthetic at all, but local infiltration or pudendal block afforded excellent analgesia for the operation. Mr. Flew thought that about 70% of primigravidae and 20% of multigravidae required episiotomy, but it might not need to be repeated in subsequent labours. In conclusion, he emphasized the necessity for careful apposition of the incised tissues at repair, not only because it made for good surgical practice, but also because it was important for the future marital happiness of the patient.

In the subsequent discussion Dr. MERVYN GOODMAN (Liverpool) stressed the importance of having a good light and adequate exposure in the lithotomy position for repair of the perineum in domiciliary practice. Dr. A. S. VALENTINE (Sierra Leone) and Mr. S. BENDER (Chester) also spoke.

Use of Pessaries in General Practice

Dr. R. H. D. LAVERTY (Coventry), a vice-president of the Section of General Practice, then took over the chair, and Mr. W. G. MILLS (Birmingham) traced the history of the use of pessaries in the vagina from early times. In the first part of the nineteenth century it was said that there were two fortunes to be made out of gynaecology—by those who inserted pessaries and by those who removed them. To-day, although a prolapse or a retroversion causing symptoms could usually be easily cured by surgery, indications for pessary treatment still existed. Thus a pessary might be used as a temporary expedient for postnatal retroversion or pelvic floor relaxation as well as in patients awaiting operation. A pessary could also be used diagnostically to ascertain whether symptoms were or were not due to an associated displacement. The permanent use of a pessary might be indicated in the aged or infirm, but was not satisfactory in certain circumstances, such as when it was easily extruded or caused pressure symptoms or excited a local reaction. The pessary of choice for prolapse was nearly always either round or oval in shape; the fitting of other types (such as the Simpson shelf pessary for procidentia) fell in the field of the specialist. The traditional type of instrument made of compressible material covered with rubber commonly caused a vaginitis with offensive discharge. This could be avoided by using the modern plastic type, which was particularly easy to insert and remove if made of soft polythene.

The patient with a permanent pessary should be re-examined within three months to ensure that the instrument fitted properly and relieved the symptoms. Douching was unnecessary in most cases with plastic rings, but the doctor should inspect the vaginal walls regularly and change the ring for a different size as necessary. In exceptional cases an early prolapse in a post-menopausal woman appeared to be cured by the use of successively smaller rings. Mr. Mills concluded by summarizing that, while the gynaecologist was responsible for deciding that a pessary was indicated and for the initial fitting, subsequent care belonged to the general practitioner.

Dr. G. I. WATSON (Peaslake, Surrey) and Mr. J. D. LLEWELLYN-JONES (Malaya) contributed to the discussion on Mr. Mills's paper.

Brandt-Andrews Technique for Delivery of Placenta

Mr. NORMAN KIMBELL (Peterborough) described the technique for delivery of the placenta which had been described independently by Brandt in 1933 and Andrews in 1940. This method reduced blood loss in the third stage, the

average duration of which was only 8–9 minutes. The most important signs of placental separation were the onset of bleeding from the placental site and a change in the shape of the fundus from discoid to globular. A hand was placed on the patient's abdomen, so that the thumb was parallel to the symphysis and the palm and fingers were on the front of the uterus just above the pubes. Holding the umbilical cord taut, a gentle upward push was made on the uterus without trying to grasp the organ. If separation of the placenta had not taken place, the cord would be drawn upwards. If separation had occurred, the cord would not rise and the uterus could be pushed upwards while gentle cord traction was made to deliver the placenta.

The routine use of ergometrine intravenously, or intramuscularly combined with hyaluronidase, at the close of the second stage increased uterine tone and enabled the placenta to be delivered by the Brandt–Andrews technique within 5 minutes in most cases. The method, the technique of which Mr. Kimbell illustrated by a film, had been used in over 5,000 cases in the Peterborough area since July, 1954, by both midwives and doctors. Sometimes it had obviated the need for manual removal of the placenta from a woman admitted from the district for that purpose. It had saved many hours of midwives' time, but had not increased either the postpartum haemorrhage rate or the number of cases requiring manual removal of the placenta, nor had inversion of the uterus followed in any case.

Mr. Kimbell replied to questions from Dr. MERVYN GOODMAN (Liverpool), Dr. K. G. DICKINSON (Birmingham), Dr. A. FULLERTON (Batley), Miss JEAN HALLUM (Birmingham), Mr. W. G. MILLS (Birmingham), Miss ELSIE WARREN (London), Dr. H. C. W. BAKER (Birkenhead), Dr. H. W. DONOVAN (Birmingham), Dr. G. I. WATSON (Peaslake, Surrey), and Dr. ROSITA RIVERA-RAMIREZ (Philippines).

SEVENTH INTERNATIONAL CANCER CONGRESS

LONDON, JULY 6–12

The Seventh International Cancer Congress was held at the Festival Hall, London, from July 6 to 12, under the auspices of the International Union against Cancer. It was opened by the DUKE OF GLOUCESTER and attended by 2,500 delegates from 64 countries. The president of the Congress was Sir STANFORD CADE, senior surgeon of the Westminster Hospital. The chairman of the British Organizing Committee was Dr. RALSTON PATERSON, and the secretary-general of the Congress Professor R. W. SCARFF.

The main part of our report consists of dispatches from five special correspondents each of whom reviews a principal subject of discussion. The programme included plenary sessions on cancer control, hormones and cancer, carcinogenesis, and the chemotherapy of cancer; lectures by Professor L. BUGNARD (Paris), Dr. CHARLES HUGGINS (Chicago), Professor V. R. KHANOLKAR (Bombay), and Professor L. KREYBERG (Oslo); experimental and clinical group and sectional meetings; sessions arranged by the International Union; and many proffered papers.

Presidential Address

At the opening ceremony on July 7, Professor J. H. MAISIN (Louvain), president of the International Union, installed Sir STANFORD CADE as president.

The purpose of the Congress, said Sir STANFORD in his presidential address, was to take stock of present knowledge on cancer, analyse the accumulated facts, and critically review the different opinions on debatable points. The Organizing Committee had chosen for consideration what he would term "the front-line advance in cancer research" and the most urgent, important, and promising clinical subjects. Picking out certain of these for comment, Sir Stanford noted the ever-increasing role of biochemistry in cancer research; the reasoned thought which was resulting in sounder surgical judgment—"the concept of cancer as a biological disturbance and not merely as a tumour has resulted in surgery being more selective, more discriminating, and serving perhaps a fewer number of patients but to a better purpose"; radiotherapy, which had achieved broader, safer, and more effective reaches of usefulness; and the development of chemotherapy, which alone, or in combination with surgery, or even as an umbrella against implantation of cancer cells during operation had widened the group of medicinal remedies against cancer. Hormonal regulation of cancer of the breast and prostate had made no longer tenable the belief that cancer is autonomous, uncontrollable, and independent of the normal physiological processes. There was a crescendo of progress from the cruder methods of surgical ablation, once the only weapon, to the more selective action of radiation, applicable to an increasing number of patients, the specific effect of chemical substances useful in a limited group, and the physiological methods of hormonal control in two sites.

Progress in early diagnosis was slow; it depended upon the doctor's awareness of cancer and the patients' belief that early advice was always to their benefit. Even prevention of cancer was not beyond the hope of achievement. To-day cancer was indeed "captain of the men of death." It was the universal enemy of mankind. It called for a united international effort.

At the close of the Congress it was announced that the Eighth International Cancer Congress will be held in Russia in 1962. Professor ALEXANDER HADDOW has been nominated president-elect.

I.—CARCINOGENESIS

In the field of non-viral carcinogenesis it is fair to say that no startling new advances were reported. After listening to a number of individual reports, and several general lectures and discussions, one was left with the impression that the various groups of workers in this field are less rigidly divided in their outlook than formerly. The point was made on several occasions that cancer may arise in many ways and that the common factor, if there is one, is to be looked for not in the properties of the agents, exogenous or endogenous, which produce it, but in the type of disturbance which they produce. This disturbance was variously described: a continually stimulated proliferation without the inhibition which normally follows seems its most general property. This may result simply from separation of tissue from its normal contacts, as in the connective-tissue tumours which develop close to plastic or metal sheets implanted subcutaneously in rats by Dr. and Mrs. E. T. OPPENHEIMER and their colleagues (New York), and others, or in pituitary glands implanted subcutaneously in normal mice by Professor O. MÜHLBOCK (Amsterdam), or merely by long-continued culture of tissues *in vitro*. Interference with one of the normal feed-back systems has a similar effect, as in the various cases of tumour development in endocrine glands produced by diversion of their secretions or removal of their target organs, as described by Dr. J. FURTH (Boston) and Professor F. BIELSCHOWSKY (Dunedin).

Mode of Action

That carcinogens often act not directly upon the cells which become neoplastic but on some other tissue or tissues was the conclusion to be drawn from a number of different observations. Dr. H. S. KAPLAN (San Francisco) developed this general theme. Of the examples of such action perhaps the most striking is one which he himself has described—namely, the development of lymphomas in normal thymus glands transplanted to thymectomized, totally irradiated mice. These tumours are sometimes of host, sometimes of donor, origin; in the latter case carcinogenesis is certainly indirect, since the graft has not been irradiated. Some observations of Professor J. W. ORR (Birmingham) brought further support for the hypothesis of indirect action.

In order to bring chemical carcinogenesis into line with this general scheme various theories were put forward. That

of the Madison, Wisconsin, school was represented by Dr. C. HEIDELBERGER and Dr. V. R. POTTER. It assumes that carcinogens combine specifically with certain essential cell proteins, which are then eliminated from the cell. The loss is permanent, and results in uncontrolled growth. Exactly how is not stated. Dr. POTTER suggested a possible mechanism—namely, that a biosynthetic pathway might be stimulated by the deletion of a competing katabolic pathway. He and Dr. S. WEINHOUSE (Philadelphia) agreed that Warburg's theory that the carcinogenic change consists of an irreversible damage to the respiratory mechanism of the cell is no longer tenable. This is a highly speculative field; moreover, the main evidence on which the theory of specific protein deletion is based has been severely criticized, notably at this congress by Dr. D. L. WOODHOUSE (Birmingham), who showed that the case for specific union between carcinogens and cell proteins is not as firmly established as was claimed. Another criticism of a theoretical kind is that since the cellular change produced is heritable it must involve nucleic acid, and, whereas it is known that transmissible "information" can pass from nucleic acid to protein, there is no evidence that the reverse procedure ever occurs. Those that use this argument conclude that the essential attack of a carcinogenic agent is on the nucleic acids, and that alteration or loss of proteins must be secondary or incidental, although quantitatively greater.

Another view, which is constantly reappearing in new forms, is that carcinogens increase the frequency of mutations, assumed to be occurring at a low rate in normal somatic tissues, which confer on the mutant cells a selective advantage in resisting normal growth controls. Sir MACFARLANE BURNET (Melbourne) developed this theory, and expressed the opinion that the study of cancer as a problem in population genetics is likely to be fruitful.

The two-stage theory of carcinogenesis received rather less attention than in recent years. Professor K. SETÄLÄ (Helsinki), who has previously reported a tumour-promoting action on mouse-skin of very large doses of certain commercial surface-active substances, described similar effects by specially synthesized substances of this class where the presence of impurities could be virtually excluded. These observations have caused concern for some years because of the increasing use of surface-active substances as detergents and as food additives. This concern is likely to be increased by Dr. P. SHUBIK'S (Chicago) demonstration that one of these substances ("Tween 60") is weakly carcinogenic as well as tumour-promoting on mouse-skin.

Cancer of the Bladder

The debt which experimental research in this field owes to clinical observation, especially in industrial medicine, was freely acknowledged. The remarkable series of researches on bladder carcinogenesis by Dr. G. BONSER and her colleagues in Leeds and Dr. W. C. HUEPER in Bethesda, U.S.A., all derive from observations of the high rate of bladder cancer in dye workers. Dr. BONSER and Professor E. BOYLAND (London) emphasized that we now know enough about bladder carcinogens to make it reasonable to hope that we may be able to eliminate most of the potentially dangerous substances of this class from our environment, or to antagonize their action.

Aetiology of Lung Cancer

Professor L. M. SHABAD (Moscow) described the great reduction in benzpyrene content of the atmosphere of a new industrial town in Russia (Angarsk) by improved methods of fuel combustion and smoke control.

Contributions to the tobacco–lung-cancer problem were numerous. Those who spoke on this subject appeared more willing than formerly to accept the possibility of multiple factors in the causation of lung cancers. Professor L. KREYBERG (Oslo) stressed the importance, and also the difficulty, of accurate histological typing of lung tumours. His careful surveys provide a firm basis for detailed correlation between the frequencies of different kinds of lung cancer and exposure to tobacco, dusts, and other environmental conditions. The conclusion, previously suspected but now firmly established, is that only squamous and undifferentiated (oat-cell) tumours can be associated with smoking habits. Many puzzles remain: for instance, Dr. E. V. COWDRY (St. Louis) pointed out that histological changes often regarded as precancerous, such as squamous metaplasia, were at least as common in the trachea as in the bronchi, yet cancer is uncommon in the former, common in the latter. Some light relief from these serious, sometimes sombre, deliberations was provided by Professor P. R. PEACOCK'S (Glasgow) film showing the gradual conditioning of fowls and other creatures to the practice, and apparent enjoyment, of cigarette smoking: no lung tumours have so far resulted. The application of tobacco tars to various animal tissues still gives widely differing results in different hands. While tumours have been produced with whole tar, and certain crude fractions, in several laboratories, no single constituent has so far been incriminated. The view that a combination of several constituents of tar are involved, possibly in conjunction with atmospheric pollutants, is gaining ground.

Dr. R. DOLL (London) dealt with the criticisms which have been made of the statistical evidence, and concluded that a causal connexion with smoking was still the most probable explanation of the observed facts. Professor W. C. HUEPER (Bethesda) stressed the possible role of metal dusts, not only in industrial workers but also in the general population. Dr. E. L. WYNDER (New York) has been trying to modify methods of cigarette manufacture so as to reduce the hydrocarbon yield on burning. This is an approach of considerable practical interest.

Radiation Hazards

The role of radiation in the aetiology of human cancer also received attention. Dr. R. DOLL pointed out that, although acute leukaemia, monocytic leukaemia, and chronic myeloid leukaemia are positively associated with previous exposure to irradiation, a similar association in the case of chronic lymphatic leukaemia is uncertain. Both this speaker and Dr. R. H. MOLE (Harwell) were of the opinion that there is no threshold dose below which irradiation is safe. Others were inclined to believe that a threshold exists in some cases, but all were agreed that it is hard to conceive an experiment or survey likely to establish this point with certainty. An interesting contribution in this field was that of Professor N. PETROV and his colleagues from Leningrad, who reported the production of a significant number of bone tumours in monkeys by intramedullary implantation of radioactive substances, though these animals are highly refractive to the action of chemical carcinogens applied by this as well as other routes.

II.—VIRUS-INDUCED TUMOURS

In the few years since the Sixth Cancer Congress in São Paulo both the scope and the amount of research into virus-induced tumours have increased tremendously. Dr. L. GROSS (Bronx, New York) has very recently discussed the viral aetiology of mouse cancer in this *Journal* (July 5, p. 1), and it was unfortunate that illness prevented his participation at the last moment in this Congress. For the centre of greatest interest in the viral field was undoubtedly mouse leukaemia and the other tumours produced by this virus or virus-complex.

Mouse Leukaemia

Dr. GROSS has now found that 50% of young, adult C3H mice—of his "low leukaemia" strain—develop leukaemia after irradiation with 150–200 r per week for four or five weeks. Filtered extracts from such tumours were inoculated into newborn C3H mice: 11% developed leukaemia (at 13 months average age) and 5% parotid tumours (at 10 months). Cell-free extracts of normal organs of healthy adult C3H mice inoculated under the same conditions gave rise to only 0.5% leukaemia (at 17 months).

but also, paradoxically, 7.5% parotid gland tumours (at 4½ months)—which therefore arose faster than in the treated group. Serial passage of the leukaemia agents in newborn hosts was found to increase the potency to such an extent that older, suckling mice could be infected.

Since Gross's first reports in this field a number of similar observations have been made. Professor A. GRAFFI (Berlin-Buch) and his colleagues are working with a mouse myeloid (chloro-) leukaemia. The same agent was derived from a number of different, spontaneous mouse carcinomas and sarcomas—but carcinogen-induced sarcomas gave negative results. The tumour yield from the filtrates was dependent upon the age of the hosts at the time of inoculation; it fell from some 40–50% between 1 day and 11 days to 22% at 3–4 months. Splenectomy before injection of the filtrate reduced the number from 72% in the controls to 8%, but if the splenectomy was delayed for one to two months after inoculation the tumour yield rose to 54%. The filtrate appeared to contain a particulate agent with the properties of a nucleoprotein. It was not highly antigenic for mice, as hyperimmune mouse serum did not fully inactivate it, but normal rabbit serum and rabbit anti-mouse bone-marrow antiserum gave no inactivation. Attempts to culture the agent on chorio-allantoic membrane appeared to be unsuccessful during the first ten passages, but at the eleventh passage tumours were produced in 78% of the inoculated mice.

A leukaemia, serially transmissible by cell-free filtrates to adult mice, was described by Dr. C. FRIEND (New York). This disease, unlike those of Dr. Gross and Professor Graffi, is characterized by a very short incubation period of about two weeks. The agent is immunologically distinguishable from normal mouse spleen and serum proteins. Immune sera from rabbits and mice neutralize the agent's infectivity, but sera from mice with other types of transplantable or "cell-free filtrate"-induced leukaemias, and sera from man, both normal and leukaemic, do *not* contain neutralizing antibody. It is possible to immunize mice with a formalin-treated virus vaccine: 80% of the animals given three intraperitoneal vaccinations resisted challenge with either virus *or* leukaemic cells and remained completely free of the disease. A similar cell-free agent derived from the brain of a C3Heb mouse bearing a spontaneous leukaemia, and inoculated intracerebrally or intraperitoneally into adult mice of the same strain, was reported by Drs. H. M. SCHOOLMAN, S. O. SCHWARTZ, W. SPURRIER, and P. B. SZANTO (Chicago) to give a 70% yield of leukaemia.

Tissue Culture of Mouse Leukaemia Agent

These agents are intriguing enough, but Drs. S. E. STEWART, B. E. EDDY, and M. F. STANTON (Bethesda) were able to culture a mouse leukaemia agent on trypsinized mouse-embryo mince. The supernatant fluids from such cultures contained an agent which produced multiple types of tumours in 60–100% of newborn mice of two different strains. All tumour-bearing mice had pleomorphic tumours of the salivary glands, and many had up to eight other types of unusual primary tumours and lesions. The latent period between inoculation and tumour production varied from a few days to several months. Further, and yet more remarkable, this mouse-derived agent was not species specific. Tumours have also been produced in rats, rabbits, and hamsters. In the hamster—and for this animal it was not even necessary to use newborn animals—sarcomas of the heart, kidneys, and subcutaneous tissues were the commonest tumours, but many had also haemangio-endotheliomas of the liver and lungs. The agent was highly antigenic, and tumour induction in mice was completely inhibited by passive immunization with rabbit antisera.

Two other, distinctive, approaches to the subject were described by Dr. R. LATARJET (Paris) and by Dr. J. RYGARD (Copenhagen). The former has tested extracts of leukaemic Ak mouse tissues in newborn isologous mice. The appearance of spontaneous leukaemias in this strain was accelerated, and in a few cases various multiple malignant tumours appeared. The agent was resistant to enzyme digestion with proteases and nucleases, and preliminary results with inoculated purified nucleic acids from leukaemic tissue suggest that these acids may have some influence on the tumour incidence. Dr. RYGARD has found that some treatments which induce leukaemia in mice also lower their resistance to infections, and has correlated this with a depression of phagocytosis as judged by the rate of clearance of colloidal radiogold from the blood. Furthermore, he found that 2–4-day-old mice also show a low blood-clearance.

In electron micrographs Drs. L. DMOCHOWSKI and C. E. GREY (Houston) and L. GROSS (Bronx, New York) claim to be able to identify the agent in the induced parotid tumours. While Professor A. D. TIMOFEJEVSKY (Moscow) reported that he and his colleagues have observed particles 40–80 millimicrons in diameter in a large proportion of human tumours. Fewer particles were present in normal tissues. There was some evidence that these globular virus-like bodies could be cultivated, together with living tissue, on chorio-allantoic membrane, and they had a distinctive antigenic composition.

Mouse Mammary-tumour Agent

The mouse mammary-tumour agent was the subject of four communications. Dr. D. H. MOORE (New York) correlated its physical and biological properties, and in an attempt to fit in all the evidence from filtration, irradiation, diffusion, and biochemistry was forced to postulate the presence in the milk of a particulate inhibitor intermediate in size between two different active forms of the virus. Dr. H. B. ANDERVONT (Bethesda) has observed, within the past few years, the disappearance of the tumour agent from two female mice of the R III strain—i.e., mammary cancer was absent from their descendants. Current experiments are being directed to finding out whether the disappearance is a result of a change in the agent, in the mice, or in both.

Dr. M. K. DERINGER (Bethesda) produced a substrain (C3He) of strain C3H mice by transfer of fertilized ova from a C3H female to the uterus of a mated C57BL female. The young were nursed by their "foster-mother" until weaned. The new agent-free strain showed a very high incidence of hepatomas—59% in virgin females, 27% in breeding females, 38% in force-bred females, 54% in stilboestrol-treated males, and 91% in breeding males. Recent studies on the mouse mammary-tumour agent were also reviewed by Dr. J. J. BITTNER (Minneapolis).

Viral Tumour of Monkeys

A new virus producing benign fibromatous lesions in rhesus monkeys was described by Dr. C. H. ANDREWES (London) and his colleagues. A year ago at the West African Institute for Medical Research in Nigeria a rhesus monkey in an outdoor cage developed a rapidly growing nodule on the eyebrow. Within the next few months similar growths appeared on the face or limbs of 20 other rhesus monkeys and a baboon. Serial transmission studies showed that the pox-like virus produces large growths which spontaneously regress after about a month. The virus passed a 0.65 μ gradocol membrane, and smears from the growths showed abundant D.N.A.-containing elementary bodies resembling those of vaccinia. Tissue cultures of monkey kidney could be infected and the virus multiplied giving cytoplasmic inclusions and elementary bodies similar to those in the growth themselves.

Benign fibromas in Virginian white-tailed deer also have been investigated by Drs. K. R. DUMBELL (Liverpool), R. MANGOLD and L. G. MACNAMARA (New Jersey), and R. E. SHOPE (New York). This filterable agent was transmitted experimentally to other deer. The incubation period was prolonged and the regression rate high. The few experimental growths that did persist eventually approached, in size and appearance, the naturally occurring ones.

Drs. P. ROUS, S. ROGERS, and J. G. KIDD (New York) transplanted metastatic tissue from the Shope rabbit carci-

noma into *newborn* rabbits. Many tumours could be propagated serially, and extracts of some 50% of them, inoculated into the hyperplastic skin of adult rabbits, gave a few typical papillomas but no carcinomas. Papilloma virus antigen appeared, however, to be present in the transplanted tumours. A similar phenomenon was discussed by Mrs. M. L. DURAN-REYNALS (New Haven) and her colleagues. Cortisone treatment of rabbits with regressing methylcholanthrene-induced skin tumours brought about a reactivation, which reversed when the daily cortisone was discontinued. During the stage of active cortisone-induced growth, a filterable agent could be recovered which induced, both grossly and histologically, a papilloma-like lesion.

A number of interesting studies on filterable chicken sarcomas and leukoses—where a viral aetiology is unquestioned—were also reported, but there is no space to summarize them here.

Future Research

In brief, one's immediate impression is that two main factors account for the great advances reported on the viral aetiology of mouse cancers. The first is the use of newborn test animals. The second is the successful propagation of the virus in tissue culture. The latter procedure may result in a considerable augmentation of both virulence and titre. The former has an obvious corollary: that together with a search for new agents—and it may not be long before cell-free filtrates from human tumours will be shown to produce tumours in mice and hamsters—a close study should be made of the reactions of newborn animals to antigenic "insults" of this kind, and, in particular, to the possibility of the animal having acquired an immunological tolerance to a "latent" agent.

III.—IMMUNOLOGY AND IMMUNOGENETICS

Present attempts to discover immunological differences between malignant and normal cells may be expected to shed light on the aetiology of cancer and perhaps also, in the future, on its treatment. Much experimental work in this field involves of necessity the study of tumours that can be serially transplanted, which in turn demands the use of pure lines of animals. Members of such inbred strains, like identical twins, have the same genetic and antigenic constitution. Until very recent times it was only from the mouse that such stocks had been raised, and this is why such extensive use has been made of this species.

Antigenic Changes in Cancer Cells

Recent hypotheses relate malignancy to the *loss* of cellular components which, it is postulated, are essential to the normal control of cell multiplication. On the other hand, the finding of *additional* antigenic components in virus-induced tumours is hardly unexpected. Their appearance in other tumours, whether indicative of virus action or not, raises distant therapeutic possibilities. For it is clear that tumours, unlike normal tissues, may survive and grow despite certain degrees of antigenic disparity between them and their hosts. In such experimental situations passive and active immunization have been effected. In fact Dr. G. D. SNELL (Bar Harbor) described such a procedure in his further analysis of the genetic factors influencing the transplantability of tissues in the mouse. He used paired inbred strains whose selected genetic (and hence antigenic) differences were too slight to cause the mutual rejection of grafted tumours. But prior immunization of one strain with the normal tissues of the other protected the host from otherwise fatal tumour grafts from the partner strain. He has used this method to investigate minor antigenic differences which would cause rejection of a skin graft for example, but which do not suffice to destroy genetically comparable tumour tissue.

Several investigators have attempted the production of antibody fractions directed specifically against tumour antigens. Dr. I. L. SPAR and his colleagues (Rochester, U.S.A.), using a radioactive label, showed that such preparations when injected into tumour-bearing animals may be selectively taken up by tumour tissue. However, it was by no means certain that this occurs as a result of the simple immunological reaction originally proposed. Be that as it may, the suggestion that such preparations may serve as carriers of radioactive or chemotherapeutic agents and bring about their concentration in the target cells is a hopeful one.

The acquisition of *new* antigens is not of course incompatible with *loss* of others. Dr. E. WEILER (Pasadena) demonstrated the disappearance of organ-specific antigen (antigen common to the species but peculiar to a particular tissue) from the liver of rats during the evolution of chemically induced hepatomas and, similarly, from the kidney during the development of stilboestrol-induced renal carcinoma in the hamster. He has recently shown that this latter antigen is apparently lost within a very short time in tissue culture, probably after only a few cycles of cell division. He finds that these antigens are confined to normal liver parenchymal cells and normal renal tubular epithelial cells respectively—that is, to the cells from which these tumours arise. There is as yet no evidence that this loss is in any sense a causal rather than a secondary event, nor that it has any bearing on the changes, possibly allied to malignancy, which accompany the derivation of continuously propagated lines of cells from normal tissue in culture.

Serological Test for Tumour Antigens

Professor L. A. ZILBER and his associates (Moscow) have used an ingenious and sensitive technique for the detection of additional antigens in human and animal tumours (including a chemically induced hepatoma of an inbred strain of mice). Guinea-pigs are sensitized to fractions of tumour tissue and later desensitized with comparable fractions of normal tissue. They are then challenged with the tumour fractions. Anaphylactic reactions denote residual sensitivity to antigen(s) absent from the desensitizing preparations. Their results with this and other methods lead them to recognize that the appearance of these new antigens may be accompanied by some loss of normal tissue antigen, but they at present differ from Dr. Weiler in their views on the extent to which organ-specific antigens are affected.

Reports by Professor G. KLEIN and Drs. E. KLEIN and K. BAYREUTHER (Stockholm) indicate that other kinds of antigens may be suppressed. Their methods enabled them to detect variants from among the cell populations of sarcomas arising in hybrid mice. By transplantation and other tests they showed that, in some tumour-cell lines so derived, iso-antigens (cellular antigens present in some but not all strains of the species) are either lost or suppressed. This is in keeping with extensive previous work on the apparent loss of iso-antigens by tumours in the course of serial transplantation. It also draws attention to the heterogeneous nature of tumour cell populations and the influence of intercellular variation and selection in the successive stages of their evolution towards increased autonomy. These workers made the striking observation that each new sarcoma displayed individual characteristics in the production of variants, although all were histologically similar and had been induced by the same dose of carcinoma in the same tissue of genetically identical mice. By contrast Drs. L. SACHS and M. FELDMAN (Rehovoth, Israel) support the view that in some instances tumours can acquire *increased* "antigenicity" in response to immune reactions, enabling them to neutralize the host's output of cytotoxic antibodies.

Interpretation Must be Cautious

Some account of current misgivings is perhaps as important as accounts of current research. Dr. P. GRABAR (France) pointed out the need, particularly important to aetiological concepts, to distinguish between absolute and merely quantitative changes in tumour tissue. Dr. T. S. HAUSCHKA (U.S.A.) and Dr. P. A. GORER (London) both

emphasized the difficulties in interpretation inherent in the use of long-established tumours of non-inbred animals: these are situations where antigenic incongruity may be present from causes unrelated to malignancy. The findings of Dr. J. G. KIDD (New York) are a warning against hasty immunological judgments. He observed the protective effect of antibody, prepared in rabbits against a mouse tumour, which he had coupled by azo-linkage with arsenic. In control experiments mice were given arsenic linked with (presumably) immunologically inert protein such as horse globulin. Surprisingly, these combinations were also protective although the two constituents, unlinked, were not.

A purely pragmatic conclusion may be drawn from the introductory remarks of Dr. Hauschka. The possibility that in some instances at least the cancer patient possesses the means of immunological resistance—which, however (and perhaps in the nature of the disease), is ineffective—is supported by scant but convincing evidence. If this should be confirmed it may be profitable to seek means of enhancing this resistance.

IV.—CHEMOTHERAPY

During the Congress some new types of potential anti-tumour drugs were described, but these still await clinical evaluation. In the main, modifications of established types of alkylating and antimetabolite drugs were reported. The clinical value of antibiotics and corticosteroids also received attention, but perhaps the most important discussions were those on how best to administer anti-tumour chemotherapy.

Modes of Administration

One topic that provoked a lively discussion was the use of chemotherapy as an adjuvant to surgery, the object being to limit cytaemia and subsequent metastases. Professor P. RUBANYI (Budapest) advocated both pre- and post-operative treatment with mannomustine ("degranol") and had observed no interference with normal wound healing. Dr. R. GROSS (Marburg) had used "B 518" as a post-operative measure, observing no depression of granulocytes below 2,000 or other undesirable side-effects. Dr. J. F. BINKLEY (Oklahoma) reported perhaps more equivocally on ten years' experience of nitrogen mustard as an adjuvant to cancer surgery, whilst Dr. H. SATO from Japan showed, in an experimental paper, the complete suppression of metastases in mice by "nitromin" administration following the surgical removal of tumours induced by subcutaneous transplantation of ascitic hepatomas. However, in the discussion, interference with normal granulation and the appearance of abscesses during healing were reported in cases where excision of a bronchial carcinoma was followed by nitrogen mustard treatment.

The influence of combined radiation and chemotherapy on survival time after diagnosis in patients with Hodgkin's disease and chronic myeloid and lymphatic leukaemia was analysed by Professor L. HEILMEYER (Freiburg). Cases treated with radiation alone survived longer (54.5 months) than those receiving combined radiation and chemotherapy (46.3 months). Those treated only by chemotherapy had the worst expectation (42.2 months). He made the point, however, that the cases receiving only radiation were, in the main, those with the least generalized condition. Dr. E. T. KREMENTZ (New Orleans) described a method of giving a chemotherapeutic agent locally by regional perfusion through an extracorporeal circuit. He isolates a limb by perfusing into the artery and out of the vein. As an example he described a patient with lympangitic recurrence of malignant melanoma in the leg who responded well for seven months to phenylalanine mustard administered by this method.

Professor L. LARIONOV (Moscow), said that with proper administration and early treatment very long remissions indeed could now be achieved with chemotherapy. He advocates working as close to the maximum tolerated doses as possible, starting chemotherapy early and before radiation, maintaining treatment at a level often determined from the patient's blood picture, and ceasing to be worried by a moderate leucopenia (2,000–3,000). He told of four leukaemic patients, all active and well after 9–10 years of maintenance chemotherapy.

Antimetabolites and Alkylating Agents

Among the new types was "kethoxal," described by Dr. A. FURST (Stanford). This ketoaldehyde, a potential antimetabolite in the Krebs's cycle, was active against the Ehrlich ascites tumour in mice. Dr. F. A. FRENCH (San Francisco) said that the bis-guanylhydrazones and bis-thiosemicarbazones derived from kethoxal-type compounds had similar activity. Dr. V. RILEY (New York) had studied the reactions *in vitro* between diamines and a melanoma metabolite, dihydroxyphenylalanine. After demonstrating a specific oxygen-absorbing reaction he went on to establish that the phenylenediamines are capable of inhibiting the Cloudman melanoma in mice.

Another new approach was that of Dr. M. B. SAHASRABUDHE (Bombay). From an analysis of the role of pyridine nucleotides (P.N.) in the production of energy, and from the fact that a tumour continues to grow despite low P.N. levels, he concluded that a tumour derives its energy via an alternative pathway—the hexose-monophosphate oxidation. Interference with this metabolic pathway should be possible by thiophene-2:6-dicarboxylic acid, and this compound has, in fact, now been shown to inhibit growth.

Among new modifications of earlier types, the use of mannomustine was described by several Hungarian delegates. This chloroethylamine derivative of mannitol had proved much less toxic than other chloroethylamines. Professor RUBANYI, as noted above, described its use in surgery, while Dr. A. ECKHARDT, also of Budapest, reviewed its use in the treatment of malignant lymphoma and leukaemia. An analogous compound, a bis-methane sulphonoxy ester of mannitol (C.B. 2511), was reported by Professor A. HADDOW (London), and similarly it was much less toxic than busulphan, to which it is chemically related. From Moscow Professor LARIONOV reported the synthesis and preliminary trials of a range of peptides of "sarcolysine," and he showed that changes in the peptide moiety were accompanied by variations in the behaviour of the resultant drug towards different experimental tumours.

There was considerable interest in the 5-fluoropyrimidines—one of the more recent additions to the antimetabolite field—and both Dr. R. DUSCHINSKY (New Jersey) and Dr. C. HEIDELBERGER (Madison) reported experimental studies, especially with 5-fluorouracil. One of its biological effects was its incorporation as a nucleotide into a "fraudulent" nucleic acid. Another uracil antagonist reported by Dr. E. FREI (Bethesda) was 6-azauracil, but its high neurotoxicity marred its clinical trial. On the other hand, Dr. A. R. CURRERI's (Madison) account of the clinical trial of 5-fluorouracil was encouraging. It had produced improvement in 13 out of 15 cases of mammary carcinoma and in 5 out of 18 cases of cancer of the colon and rectum. Hepatomas and ovarian tumours also responded.

Antibiotics and Corticosteroids

Whilst accounts of the earlier antibiotics azaserine and "DON" were noticeably missing, two clinical reports were given on actinomycin D. Dr. CHARLOTTE TAN (New York) described responses observed in the treatment of 95 children and 15 adults with metastatic neoplasms. None of the adults showed any therapeutic response, but at near toxic doses objective responses lasting up to four months were observed in children with Wilm's tumour, neuroblastoma, and nephroma. Both Dr. TAN and Dr. S. FARBER (Boston) told of the apparent sensitizing of radio-resistant rhabdomyosarcomas by combining radiation treatment with intra-

venous injection of actinomycin D. Dr. Farber also mentioned as promising a Japanese antibiotic, "mytomicin."

The role of corticotrophin, cortisone, and prednisone in the management of chronic lymphatic leukaemia was discussed by Dr. R. BODLEY SCOTT (London), who pointed out that their usefulness depends on their ability to prevent haemolytic anaemia by supressing the auto-immune reaction of erythrocytes. Dr. J. G. FREYMANN (Boston) maintained, however, that there was no correlation between the life-span of erythrocytes and corticosteroid response.

V.—CONTROL OF CANCER

Cancer control is an intricate business, depending for its success on an alert and well-educated professional group, a co-operative and informed public, and the availability of adequate diagnostic and therapeutic services. This point of view, put forward by Dr. J. R. HELLER (Bethesda), seems reasonable when it is realized that cancer has risen over the past 50 years from the eighth to the second major cause of death in the United States, where it is now regarded as a national health problem. There the so-called "seven danger signals" of cancer are widely advertised, publications on cancer are freely available, and a regular annual check-up is advised.

Early Diagnosis

Professor B. W. WINDEYER (London) discussed the same problem as encountered in Britain. While he thought that much more could be done, he did not agree with all the measures adopted in the United States. The key figure in cancer control must be the general practitioner, and better control should follow better medical education. Education of the British public should be approached differently. Group surveys showed that delays in the patient attending were due to ignorance or fear, and slogans based on fear might well have an adverse effect. The most important prognostic factor was the biological behaviour of a tumour, and, if the public were encouraged by misleading slogans to believe that early diagnosis must lead to cure, disappointment and a loss of confidence in the medical profession would result. Special cancer centres were only advantageous if enough pre-malignant lesions and early cancers were discovered at them to justify their extra cost; moreover, their provision might lead to a loss of confidence in the general practitioner, which would be extremely unfortunate. Public education was worth while, but preferably by talks to small groups of normal people. The aim should be to remove false ideas rather than to instil half-truths and inaccurate slogans. Cancer education should be considered part of a general programme towards the betterment of the nation's health.

Dr. RUTH GRAHAM (Buffalo) opened a discussion on exfoliative cytology. Its value in the diagnosis of early cancer of the cervix depended on the population screened. It was reasonable, for example, to exclude women under 30 and Jewesses and to concentrate on women with symptoms, those married before 20, and the lower social classes. The average yield over the United States was now 4.7 per 1,000 patients examined. Professor H. C. MCLAREN (Birmingham) believed that expert technicians, treated as members of a team, were more than adequate for the work. He treated carcinoma *in situ* in young or pregnant women by conization of the cervix and careful follow-up, as this allowed normal parturition and a more radical operation could always be undertaken later if necessary. Dr. L. V. ACKERMAN (St. Louis) felt that cytological examination of the sputum was now so reliable that, if the test was positive, peripheral lung tumours could be removed by lobectomy without prior biopsy through the lung and the consequent risk of pleural implantation. Professor J. B. DUGUID (Newcastle upon Tyne) had found examination of gastric washings of great value in establishing the diagnosis of gastric cancer. Last year 850 patients were examined and 60 reported positive. All were confirmed at operation, and in four the growth was little more than microscopic in size; in only four cases was carcinoma missed.

Treatment of Bladder and Breast Cancers

Bladder cancer is increasing in frequency, and the suggestion that the main aetiological factors are now known is most encouraging, making the disease in this respect similar to bronchial cancer. Whether either disease will prove preventable remains to be seen. The panel discussing the present-day treatment of bladder cancer covered most aspects of the problem. Mr. D. M. WALLACE (London) thought the infiltrating lesion without fixation or widespread disease was the only really difficult therapeutic problem. Radioactive implants or supervoltage *x* rays were usually indicated, followed by total cystectomy if necessary. Partial cystectomy was useful only if the disease was limited to a small area of the dome or the side of the bladder without involving the ureter. Dr. G. W. BLOMFIELD (Sheffield) reviewed the place of radiotherapy. Dr. C. FRANKSSON (Stockholm) described the construction of an artificial bladder after total cystectomy, which allows micturition through the urethra.

The treatment of breast cancer was covered in detail at one clinical group meeting and separately by several other speakers. The most notable features were the general acceptance of the limitations of surgery, an increasing confidence in the value of radiotherapy, and the failure to agree on the particular indications for any particular form of hormone therapy. Dr. C. D. HAAGENSEN (New York) emphasized the need for careful case selection before embarking upon surgery. In his clinic they relied on the radical Halsted operation for patients in the early stage. Professor D. W. SMITHERS (London) said the histological grading of the tumour was the most important factor in prognosis; others were its site, the age at onset, and mode of spread. Mr. R. S. HANDLEY (London) described his most recent findings relating spread to the internal mammary chain and the prognosis.

Several speakers discussed the hormonal treatment of breast cancer. All differed somewhat, but all agreed that it was quite impossible to forecast exactly whether or not a tumour would respond to any particular measure. Dr. R. LUFT (Sweden) had the impression that hypophysectomy was probably more effective than adrenalectomy. If a patient was premenopausal or not more than one year postmenopausal, he recommended oophorectomy as the first step, followed later by major endocrine surgery if necessary. Five years or more after the menopause simple oophorectomy was not effective and large doses of oestrogens should be tried, with endocrine surgery later if needed. Androgens were not often indicated and in his experience were effective only in 20% of cases. Hypophysectomy induced a regression in about 50% of cases. This subject was also covered by Professor C. HUGGINS (Chicago) in his Congress lecture; the experimental background was discussed by Sir CHARLES DODDS (London). The programme of radiotherapy recommended by Dr. F. BACLESSE (France) was generally accepted by all speakers as an effective method of treatment, but the impossibility of forecasting accurately the radiosensitivity of a particular tumour makes surgery the best hope for cure where the disease is strictly local.

Bronchial Carcinoma

Bronchial carcinoma remains a most depressing disease to treat, although it is true that radical surgery occasionally achieves an excellent result. Radiotherapy is almost entirely palliative. A remarkable series of cases, however, was reported by Dr. GWEN HILTON (London). She has treated 38 carefully selected patients by radical radiotherapy alone, and 8 of them have lived for 15 years with no recurrence. This result is all the more important when it is realized that all cases in the series were classed as operable. Her figures may therefore be compared directly with those of surgery.

Motoring News

DEPRECIATION

The eternal problem of counteracting wear and tear on motor-cars confronts us all at some stage or another, and there comes a time when decisions have to be made on whether the car should be done up or exchanged for a later model. Car dealers have never been the most popular members of the community, for they are often accused of making large sums of money out of the simplest of business transactions. But they have to live, and, though a few do make big money, trade is seasonal and they sometimes have to cover their losses on narrow profits. The wise car-owner can therefore take advantage of this if he chooses the right time of year to trade-in his used model.

The owner of a small popular model has little to fear from the dealer, because the resale value of modern cars of low horse-power is very high. Demand is great because of their economy and low insurance rates, and they can still be sold easily third- or fourth-hand.

The financially economical period of use for a small car such as a Morris Minor is, in theory, about two years. After this time its basic value begins to drop off, depreciation figures on tax accounts begin to level off, and repair charges loom ahead. The more expensive car, say one costing just over £1,000, retains its value only if it is a popular model which is reasonably economical for its size and is not likely to be superseded by a new model in the near future. A typical example of a car in this group which is selling well at present is the Austin A90. Care is needed when buying the more expensive type of car, since the greater the initial cost the more will the price drop when selling time comes round.

As to the medium-priced luxury models, of which the Rover range are among the best sellers, five years would be an economical period of ownership for a car of this sort if the user is to recover the considerable initial outlay by way of lower repair charges on a quality model which will last well for a number of years. In fact, by careful buying and selling, cars in this class can sometimes be sold after five years for very substantial sums if they have been carefully looked after, often for as much as would be realized on the sale of two cheaper smaller cars used over the same period. But this may be exceptional; it happens to apply to Rovers, while the less popular luxury models often lose value quickly. Buyers of this type of car can afford to buy them new, and second-hand prices have to be slashed to attract the small minority of purchasers who just cannot afford the new price. Though petrol consumption has to be taken into account, many G.P.s find it no more of a financial burden to run a large car and claim considerable tax relief on heavy garage bills than to suffer the relative discomfort of an economy car with the correspondingly small tax allowance on fuel and repairs.

In most cases favourable part-exchange terms are obtained by disposing of a car in favour of a similar new model, preferably through the same dealer as supplied the old one. In this way the trade-in loss covers the running costs for, say, two years, and one starts off with a new model again. This process has to be kept up, however, for if the gap between new and old is allowed to grow then the price gap becomes too great. Many country doctors doing large annual mileages adopt this scheme; the cars are supplied and serviced by the dealer concerned and exchanged at a prearranged price.

Car Radios

There are no hard-and-fast rules about which radio sets perform best in which cars, and, unless the makers them-

(*Continued at foot of next column*)

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Sandosten+Calcium (Sandoz Products Ltd.).—Sandosten is the proprietary name of the antihistamine drug thenalidine (or thenophenopiperidine) tartrate, and it is recommended that it should be given in conjunction with calcium. Tablets are available each containing thenalidine tartrate 25 mg., calcium lactate 579 mg., and calcium gluconate 794 mg. This antihistamine drug is also marketed in ampoules for intravenous injection, in an ointment, a syrup, and a nasal spray.

This combination does not seem to have been tried extensively in Great Britain and the reports of clinical trials emanate from the U.S.A. Internal treatment, with or without local application of the same substance, is reported to have given the best results in allergic rhinitis, but good results also in allergic skin conditions, notably contact eczema, atopic eczema, and urticaria. The duration of action is four to six hours, so that treatment should presumably be given three or four times daily. The few published clinical trials report a very effective action combined with the minimum of side-effects and toxicity.

N.H.S. basic price: 100 tabs., 19s. 8d.

Debendox (Riker Laboratories Ltd.).—Each tablet contains dicyclomine hydrochloride 10 mg., doxylamine succinate 10 mg., and pyridoxine hydrochloride 10 mg.

Since the exact pathogenesis of pregnancy sickness is still unknown, a variety of drugs is being used to counter or prevent it and to reinforce dietary and other advice. The drugs fall largely into three groups—sedatives and antispasmodics, antihistamines, and B vitamins—and there are several proprietary preparations which contain a combination of different drugs from the three groups, as does debendox. Dicyclomine hydrochloride is an antispasmodic, weaker than atropine and having some local anaesthetic action. Its value in the treatment of peptic ulceration and for conditions of increased gastro-intestinal mobility has been reported on favourably. Doxylamine succinate is one of the less active but longer lasting antihistamines. Pyridoxine is vitamin B_6. The tablets are coated so that absorption is delayed and the anti-emetic action takes effect four to six hours after ingestion. The recommended dose is therefore two tablets at bedtime so as to counter the early morning attack which is the usual, but not constant, feature of pregnancy sickness.

N.H.S. basic price: 100 tabs., 38s.

(*Continued from preceding column*)

selves specify a particular set, trial and error is really the best method of finding them, particularly portables. The small battery–mains portable or transistor models are ideal for use in the car, and they can be taken out for picnics or home use. Battery-mains models will give better reception in a car than battery-only examples. Built-in sets are now available with push-button controls even in the cheap cars. They are a much better buy than manual-tuning sets because there is little difference in the price and the cheapest push-button ones give very good reception. Those fitted in Rover and Humber cars are really good and are well worth the money asked. The Ekco radios on Fords give good reception, though most have manual tuning. Aerials, like the sets, vary too, and their positioning for best results depends largely on where the car is being used (since certain parts of the country have better radio reception than others) and on the set fitted.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Ectopic Pregnancy after Pelvic Tuberculosis

SIR,—Tuberculosis of the female genital tract is a comparatively frequent cause of infertility, and, although the incidence may not be increasing, modern diagnostic methods have allowed the condition to be discovered more often. The finding of an active tuberculous lesion in the endometrium may be associated with gross pathology in the Fallopian tubes and there may be corresponding symptoms of pain and heavy periods. In many cases, however, there is no complaint beyond the infertile marriage. Treatment has been completely altered by modern chemotherapy. Surgical removal of the pelvic organs was formerly practised with some success, but conservative surgery frequently led to fistulous complications, while radical removal could on occasion prove extraordinarily difficult. The patient with quiescent disease would often remain untreated. It was natural that streptomycin and allied drugs should be adopted as an alternative to surgery, and this conservative medical treatment is now widely used.

It is the purpose of this letter to draw attention to a complication of this medical treatment that has not received sufficient notice. I refer to the increased incidence of ectopic pregnancy among these patients, and I attribute this directly to the resolution of the active tuberculous salpingitis that accompanies many (if not all) cases of endometrial tuberculosis. Unfortunately the tube seems often to be left patent but inert, so that the active spermatozoa can migrate but the passive fertilized ovum cannot be propelled into the uterus. Among 29 patients seen personally with pelvic tuberculosis there have been six tubal pregnancies. The two most recent are described briefly below.

Mrs. R. S. complained of infertility after only a year of married life and had an ovarian cyst impacted in the pelvis. Her husband's seminal analysis was normal. At laparotomy (September 9, 1957) the dermoid was removed, but chronic interstitial salpingitis suggested tuberculosis, which was confirmed by culture of curettings. Treatment with streptomycin and P.A.S. and subsequently isoniazid was given and she was awaiting curettage when the ectopic pregnancy ruptured on March 20, 1958.

Mrs. M. B., aged 26, complained of infertility and vague pelvic pain. Two salpingograms showed abnormal results with inadequate tubal spill, and a diagnosis was made of chronic pelvic adhesions, probably associated with appendicitis in the past. At laparotomy on October 8, 1956, chronic interstitial salpingitis was discovered and tuberculosis confirmed on examination of curettings. Chemotherapy with streptomycin and P.A.S. was given for three months, after which curettings were proved negative. A baby was adopted, intercourse became relatively infrequent, and the tubal pregnancy ruptured on June 30, 1958.

There are patients in whom it may be right to foster the tiny hope of successful pregnancy following medical treatment for pelvic tuberculosis, but the disease will surely exact a toll of ruptured ectopics. The day may yet dawn when patients will be asked to accept the almost inevitable infertility of pelvic tuberculosis, and after adequate chemotherapy the diseased tubes at least will be removed. In the case of each patient reported above, *both* tubes were excised at operation, for which the husbands as well as their wives were demonstrably grateful.—I am, etc.,

Birmingham. WILFRID MILLS.

Ring Pessaries

SIR,—Dr. D. N. S. Robertson and Dr. F. D. Stott, in their admirable memorandum on "polythene" ring pessaries (*Journal*, July 5, p. 30), mention that they are suitable for those women for whom an operative cure would be an unwarranted risk, for those who refuse to undergo surgical repair, and for women in the midst of their childbearing, though they do state that surgical repair is the ideal method of treating this common disability. They then proceed to state the advantages of polythene over rubber and vulcanite. They make no mention of celluloid rings, which have been available from Allen and Hanburys Ltd. for many years. I have used them in a great many cases for about 12 years, and have found them most satisfactory. They are inert, produce no tissue reaction and no vaginal discharge, so that douching is not necessary. They do not compress for insertion in the introitus, but when immersed in boiling water for a few seconds they soften and can be bent to any shape, hardening immediately on cooling.

It is my experience that few women need a circular ring, that indeed a circular shape keeps the vaginal walls stretched and does not encourage them to regain their tone, while a pear-shaped support, somewhat like an Albert Smith pessary and wide enough at the base to ensure that it remains *in situ*, is easily inserted. It is always possible to make the patient completely comfortable by altering the shape—for example, to take pressure off the rectum, or give more support to the bladder. I believe that operative measures are often unnecessary where such a pessary is worn for long enough in cases of prolapse after childbirth and combined with exercises to improve muscle tone. It is usual to find that gradually a smaller size becomes necessary as the muscle tone improves, until no further support is required. I well remember one patient, a farm labourer's wife, who presented with a procidentia after her thirteenth confinement: she needed a 95 mm. ring to begin with, but gradually improved and needed narrower and smaller pessaries (she ended up with a 65 mm.), until after four years she was restored to normal and the pessary removed. It is, of course, likely that there will be a recurrence of the prolapse when such patients are much older, but at such a stage it is usually much easier for patients to submit to operation, which can create so many problems for a mother with a young family.—I am, etc.,

London, N.W.1. ELEANOR MEARS.

Cardiac Arrest

SIR,—I am interested to see in the article on cardiac arrest by Dr. D. W. Blair and his colleagues (*Journal*, June 28, p. 1521) a statement of the need for a visual pulse monitor. I have been using a simple instrument of this type for some eight years and have found it extremely useful. It was described in the *British Medical Journal* (1952, **1**, 1188), but the circuit given there has since been improved. No "electronic" parts are used in the electrical circuit, and it is cheap, portable, and easily constructed. As it does not depend on the electrical activity of the heart but on pulsation in the arterioles of the finger pulp, a severe fall in blood pressure or an ineffective peripheral circulation is shown at once and so too are cardiac arrhythmias or variations in output.

I have not been able to interest British instrument manufacturers in the device, but it is made by several firms in the United States.—I am, etc.,

Stow on the Wold. V. J. KEATING.

SIR,—Dr. D. W. Blair and his colleagues (*Journal*, June 28, p. 1521) are surely right to re-emphasize the need for vigilance in the use of neostigmine, and to attribute their case of cardiac arrest to its too-rapid injection after what might seem a possibly inadequate dose of atropine. Correctly used, neostigmine is a very safe antidote to curare or gallamine, but a sound "drill" should be adopted, such as the following:

Having decided that neostigmine is needed, atropine is given intravenously, the dose (commonly up to 1/50 of a grain—1.3 mg.) depending largely on the anticipated total dose of neostigmine which is to follow. In abdominal cases the atropine is best given just before starting peritoneal closure. Once the peritoneum is securely closed and atropine-induced tachycardia established, the pulse is timed and the state of respiratory activity (or lack of it) noted. The anticipated necessary total dose of neostigmine (usually between 1 and 3 mg. in adults) is then drawn up

and one-third of it injected intravenously. Two minutes later the pulse and respiration are again observed and the second third injected. The last fraction is similarly given two minutes later again, but each injection is preceded by observation of the respiratory activity to make sure that it is necessary, and of the pulse rate to make sure that it is safe, the aim being to have the patient leave the theatre with full respiratory activity and a slightly rapid pulse, for the slowing effect of neostigmine may outlast the accelerating effect of atropine.

The fractional technique enables one to adjust the anticipated dosage up or down to meet the exact requirement, and to give extra atropine in good time should bradycardia threaten. Most textbooks of anaesthesia are seriously deficient in detail on this point. The above procedure is very reliable and convenient in practice and soon becomes second nature.—I am, etc.,

Bristol. T. R. STEEN.

SIR,—In their account of a case of cardiac arrest (*Journal*, June 28, p. 1521) Dr. D. W. Blair, Mr. W. T. Irvine, and Dr. R. C. Taylor rightly emphasize the value of a means of continuously monitoring the patient's pulse during anaesthesia. Since, however, they appear to imply that such an instrument is not available it should be pointed out that a number of cardiotachometers have been designed.

While it is a comparatively simple matter to monitor the heart beat under optimal conditions, reliable operation is much more difficult to obtain under conditions of diminished cardiac output and when friction of towels against skin is present. One of the most useful and reliable instruments for the anaesthetist is that described by Molyneux.[1,2] This possesses no unnecessary refinements (unless one includes under this heading an audible, as well as visual, signal synchronized with the pulse) and utilizes nine transistors and four crystal diodes. The subject has recently been well reviewed.[3]—I am, etc.,

Southend-on-Sea. GORDON P. LOWTHER.

REFERENCES

1 Molyneux, L., and Pask, E. A., *Brit. J. Anaesth.*, 1955, **27**, 262.
2 —— *Electron. Engng*, 1957, **29**, 125.
3 *Lancet*, 1958, **1**, 956.

Neurological Reactions with Phenothiazine Derivatives

SIR,—The publication of Dr. E. H. Hare's memorandum (*Journal*, June 21, p. 1462) describing an unusual dystonic syndrome in a patient on chlorpromazine (3-chloro-10-(3-dimethylamino-*n*-propyl)phenothiazine) prompts me to report the following case.

On December 5, 1957, at the urgent request of a London teaching hospital, a man aged 65 who had been attending the outpatient department and "had been seen over a long period by a succession of doctors" was admitted here as an emergency case. On examination he was found to be an emaciated and very ill man. Facial tics (bilateral) caused him to grimace continually and "make faces." Involuntary twitching of the muscles of the mouth, throat, and neck caused great difficulty in articulation (spastic dysarthria) and his speech was indistinct. Every few minutes severe spasm of the left sternomastoid caused the face to be turned to the right side and the head to the ipsilateral side (spasmodic torticollis). The muscles of all the four limbs were in a state of general rigidity, more marked in the legs, while tremors and jerky contractions were more marked in the arms. He was unable to sit still, nor could he dress himself or tie his shoe-laces.

Nothing abnormal was detected in his central nervous system. The knee-jerks were very brisk, the abdominal reflex was present, and the plantar reflexes were flexor. The clinical picture was a combination of pseudo-bulbar palsy and Parkinsonism, although the facial tics and some of the gross tremor were hysterical in nature. Mentally he was quite conscious but obviously very apprehensive.

With rest in bed the acute symptoms and the dysarthria cleared up. The tics and gross tremor responded to the usual method—i.e., suggestion—leaving generalized rigidity of the limbs. He was therefore given benzhexol hydrochloride, 1 mg. once daily for three days and then 2 mg. daily for 10 days, which afforded him great relief. He was free of symptoms for several weeks and expressed a desire to return to work. As the aetiology of his acute symptoms and dysarthria was not apparent on May 1, he was given 50 mg. of chlorpromazine hydrochloride three times a day, and this dose was kept up for four days, when he felt "very well indeed." On May 5 he was given 25 mg. of promazine hydrochloride (10-(3-dimethylaminopropyl)phenothiazine hydrochloride), thrice daily, and this was continued for some days. On May 10 he went to London by train, but in the evening noticed spasm of the muscles and was unable to walk or talk clearly. He was brought back by car. Next day he could not get out of his bed at all and had a recurrence of the rigidity of the muscles of all the four limbs. He suffered from severe spastic dysarthria and could not articulate at all. Attempts to speak caused severe spasm of the neck muscles with gasping for breath. He had also difficulty in swallowing. The alarming nature of his symptoms caused much concern not only to the nursing staff but also to the other patients on the ward. Promazine hydrochloride was therefore discontinued. Within 30 hours he showed marked improvement, was able to leave his bed unaided and talk normally. He had no more symptoms until his discharge on June 6, 1958. He was an intelligent man who seems to have suffered from chorea at the age of 13 but had been passed fit for the Forces and had also served at Gallipoli.

It is only fair to add that up to 300 mg. of promazine hydrochloride daily has been given here to a large number of patients with great benefit, and no untoward reactions have been noted even after sudden withdrawal of the drug. From a single case it would not be fair to draw the conclusion that chorea in childhood was responsible for the symptoms described above. To enable doctors and nurses to recognize this condition and differentiate it from acute hysterical aphonia, a film has been prepared at this hospital.—I am, etc.,

Belmont Hospital Neurosis Centre, Sutton, Surrey. M. N. PAI.

Burns in Sterilizing Rooms

SIR,—The incidence of burns among members of the nursing staff who work in sterilizing rooms is very high. I do not think that this is due to such staff being particularly accident-prone. An examination of the conditions of work in a number of sterilizing rooms reveals a state of affairs that no inspector appointed under the Factories Act would ever tolerate. Ventilation is almost always inadequate, the humidity is appalling, and the sterilizing apparatus is of poor design and badly installed. Steam pipes are often quite unlagged, taps and handles inadequately insulated, and bowl and instrument sterilizers are capable of discharging jets of steam upon the bare arms of the passer-by.

One may wonder, also, for how much longer our surgeons, who have the use of some of the world's best surgical instruments, will continue to allow them to be ruined by boiling in hard water, instead of using hot-air sterilization as has been the practice on the Continent for very many years.

I would suggest that this is a problem that should be attacked by hospital boards with a determination and resolution equal to that devoted to the elimination of static electricity in operating theatres.—I am, etc.,

Hove, Sussex. REX BINNING.

Wrong Connexions

SIR,—One evening recently I went to anaesthetize for an emergency operation. The Boyle machine had been used since the orderly had gone off duty, so that the labels on the cylinders did not necessarily reflect their state. On opening the valves in turn, it was seen that the "wrong" rotameters registered; the connexions were checked and it was found that the two oxygen cylinders delivered to the nitrous oxide rotameter and vice versa.

The machine is of a "safe" type, with non-interchangeable Schrader connexions to the reducing valves, non-interchangeable threaded unions to the flow-meter block. Certain parts had been renewed the previous day, when presumably wrong union nuts had been fitted to the ends of the tubes. (The latter, of anti-static rubber, bore the correct identifying colours.) Two anaesthetists had used the machine in this state without remarking anything amiss. Calculation shows that when the oxygen meter showed a flow of 2 litres/minute and the nitrous oxide meter showed 6 l./min., which is a common setting, the resultant mixture would be 77% oxygen and total flow 9.2 l./min.

To check everything oneself seems pedantic, and many anaesthetists using familiar equipment in well-staffed theatres take correct function for granted, with a confidence matching that with which they drive off in their cars each morning without investigating oil and water levels. The mistake described did not have dangerous consequences but shows how careful it is necessary to be. If there had been an accident the anaesthetist would have faced H.M. Coroner.—I am, etc.,

Bramhall. R. N. SIDEBOTHAM.

Pseudo-medical Advertising

SIR,—As medical adviser to an advertising agency, I was very interested to read Dr. R. E. Dawson's comments in your correspondence columns on "pseudo-medical advertisements" (*Journal*, June 21, p. 1482). I think that he is being unnecessarily harsh on advertisers. Most large advertising agencies employ a medical adviser, who is consulted whenever the question of claims in the medical field for any product arises in connexion with advertising. Most manufacturers of medical or semi-medical products also have their own scientific advisers, and, very frequently, qualified medical advisers as well. Moreover, there are bodies whose job it is to examine claims made by advertisers, and these bodies have laid down strict rules and codes of standards which are accepted by the majority of newspapers, magazines, and other publications, as well as television interests and by far the majority of service advertising agencies. It is therefore practically impossible for exaggerated benefits to be claimed in normal advertising channels for "useless products." In addition, in the highly competitive commercial conditions applying to-day, such products would not be handled by reputable advertising agents nor would responsible retail outlets accept them for sale.

In my opinion, the public will always buy tonics, vitamins, pain-killers, and indigestion remedies because they would rather pay for them than queue in their doctors' overcrowded surgeries. If they were not aware of the availability of these products, I would hate to think what number of extra patients would waste their G.P.'s time for minor ailments. It is of course quite natural and surely not unreasonable that a manufacturer should, in his advertising, seek to bring before the public the advantages which his product enjoys over those manufactured by his competitors.—I am, etc.,

Guildford. DICK GLOVER.

Calcium and Phosphorus Metabolism

SIR,—There are several points in the article by Dr. G. L. Mouzas (*Journal*, June 14, p. 1385) which conflict with my experience of calcium and phosphorus metabolism in 230 patients with renal calculi.[1,2]

Dr. Mouzas states that only four of his patients had parathyroid dysplasia. He apparently requires to have both an elevated serum calcium and a low serum phosphorus, and hypercalciuria, to make the diagnosis of hyperparathyroidism. I have found no single test which is a satisfactory test of parathyroid function, but this does not mean that hyperparathyroidism cannot be present unless all these abnormalities are found, as Dr. Mouzas seems to imply. I have observed patients with hyperparathyroidism in whom only one of these abnormalities was present. Hypercalciuria disappears and the serum phosphorus rises again with the onset of renal failure, and in these patients a raised serum calcium may be the only biochemical sign of hyperparathyroidism. In almost all patients with hyperparathyroidism who are followed up for a sufficiently long period before operation both the serum calcium and serum phosphorus values fluctuate, the lower values often falling within the normal range. Dr. Mouzas regards a raised serum calcium alone as being of no significance. An elevated serum calcium is always pathological and deserves the most careful investigation to discover its cause. Quite apart from the tendency for these patients to form calculi again, the hypercalcaemia causes renal damage. I also have noticed the frequency with which a low serum phosphorus occurs amongst calculus patients. Occasionally a low serum phosphorus may be the only sign of hyperparathyroidism, although there are other causes of disturbed phosphate metabolism.

It is difficult to interpret Dr. Mouzas' figures for phosphate/creatinine and calcium/creatinine ratios, because the headings of his Table III appear to be transposed. He has shown by 24-hour calcium excretion studies that all patients with a calcium/creatinine ratio above 0.3 had hypercalciuria. It cannot be claimed that this ratio is an effective screening test unless it can also be shown that values below this figure were not associated with hypercalciuria. I note that in seven of his patients the value of the serum alkaline phosphatase is above the upper 1% range, although he states in the text that all were within normal limits.

I think that his interesting group of patients merit further study.—I am, etc.,

Belfast. MARY G. MCGEOWN.

REFERENCES

[1] McGeown, M. G., and Bull, G. M., *Brit. med. Bull.*, 1957, **13**, 53.
[2] —— *Clin. Sci.*, 1957, **16**, 297.

*** It is regretted that in the headings of the ninth and tenth columns of Dr. Mouzas' Table III Ca/Cr and PO_4/Cr were accidentally transposed, as Dr. McGeown points out. —ED., *B.M.J.*

Rheumatology as a Whole-time Specialty

SIR,—Dr. L. Mandel (*Journal*, June 21, p. 1482), referring to the treatment of the rheumatic diseases, stresses that the doctor must be trained "to treat the patient as a whole, and not the disease or local disability." His conclusion that treatment should be organized by a system of dual control seems, however, unlikely to achieve this object.

This approach to the problem is absurd, in this country at any rate. Consultants in physical medicine are now required to hold a higher medical degree in addition to the specialist diploma. A long training in both general medicine and physical medicine is necessary before senior status is attained. In fact, whether Dr. Mandel likes it or not, physical medicine is the specialty best suited to deal with the rheumatic diseases under the N.H.S., and, in view of the magnitude of the problem, it is hoped that the establishment of physical medicine specialists will soon be increased in order to provide adequate cover for the whole country.—I am, etc.,

Broadstairs, Kent. R. W. BARTER.

Undescended Testicles

SIR,—I was extremely interested in the paper on the results of hormonal treatment of the undescended testis by Drs. J. Brunet, R. R. de Mowbray, and P. M. F. Bishop (*Journal*, June 14, p. 1367). At the time of passage of the testis through the inguinal canal in normal descent a marked lengthening takes place in the cord without which the vas deferens would be too short to permit such a movement. The remaining testicular descent process—i.e., from the neck of the scrotum to its floor—is brought about by lengthening of the cord, particularly of the vas deferens and cauda epididymis, and of the pars vaginalis gubernaculi (which includes the cremaster muscle). These changes would appear to be under the influence of gonadotrophic hormones, either directly, or indirectly through the testis due to its androsteroid production, and the clinical results published in this paper are essentially in agreement with these views. So long as the mesenchyme of the gubernaculum testis has not been involved by fibrous tissue, which would prevent normal growth changes and anchor the testis or its covering in an abnormal manner, there seems no anatomical reason why hormone treatment should not produce the results quoted.

Mr. Denis Browne's objections to hormone treatment (*Journal*, June 28, p. 1541) do not appear to be based on the anatomy of normal testicular descent. It is unfortunate,

therefore, that he should accuse the endocrinologists of just such a lack of knowledge. As I commented last year on certain of Mr. Browne's anatomical views (*Journal*, June 15, 1957, p. 1420) I do not propose to repeat myself needlessly. I would, however, in all fairness to Mr. Browne, agree that the anatomical criteria put forward by Dr. Brunet and his co-workers would sometimes be difficult to substantiate, as they themselves admit. I would suggest that the important criteria for hormonal treatment of testicular maldescent are that the testis should be somewhere on the track of normal descent and not anchored peripherally. A testis found in Browne's "superficial inguinal pouch" is off the normal course of descent and therefore not likely to descend under the influence of hormones. The difficulty, however, appears to be that of diagnosing accurately when a testis is or is not on the correct line of testicular descent when in the external inguinal region.—I am, etc.,

London, W.C.2. K. M. BACKHOUSE.

Fatal Haemorrhage from Superficial Varix

SIR,—In our local newspaper recently a 30-year-old mother of five children was reported to have bled to death from a varicose vein in her leg. This recalled a similar death of which I had heard years ago. A tourniquet in that instance had been applied by a lay person between the heart and the hole in the vein. On hearing of another fatality, I wondered if the same mistake had again been made. By courtesy of Dr. L. Manoim, the coroner's pathologist, I was able to see the necropsy.

The body was that of a young woman about seven months' pregnant. The pale skin, pale mucous membranes, and pale organs made plain that blood loss had been severe. Her left leg was swollen. Both her lower limbs showed varicose veins, and many of these varicosities were particularly superficial, even protuberant. About 8 in. (20 cm.) above the left lateral malleolus there was a small opening into one of these extremely superficial varicosities. This opening was only of about one-tenth of an inch (2.5 mm.) in diameter. From a vein above and below it the pathologist expressed blood on to the skin through the hole. Microscopy gave evidence of ulceration at this site.

Her husband and her friends had said that through this small venous opening she had bled to death. They had applied some home-found tourniquets, towels, handkerchiefs, even bed sheeting around the leg above the hole in the vein. They thought this was the correct site for tourniquets, but, no matter how hard they had tried to compress the leg with their tourniquets, the bleeding had continued until she died.

To return to the consulting-room, patients sometimes ask if their varicosities will bleed. The chance of this is usually so small that mostly the medical attendant will be justified in giving an assurance: but, while operation is being arranged for those who require it, any who have particularly vulnerable veins can be told what to do if bleeding should occur. They should *apply pressure directly to the bleeding point*. The danger of ignorance in this matter is shown by the fate of two persons. To each a tourniquet had been applied between the heart and the hole in the vein. Such "first-aid" measures by part-trained or untrained persons are understandable, but so are the fatal results.—I am, etc.,

Launceston, Tasmania. W. W. WOODWARD.

Male Homosexuality

SIR,—I was most interested in the excellent article entitled "A Factual Study of Male Homosexuality" by Dr. R. E. Hemphill, Dr. A. Leitch, and Dr. J. R. Stuart (*Journal*, June 7, p. 1317). It was encouraging to find that others had quite independently come to almost the same conclusions as I had myself. As the authors state that "there is surprisingly little factual literature dealing with homosexuality," it would seem that my paper,[1] which would come into this category, has escaped the notice of those interested in psychological and social medicine, no doubt owing to its title, "Venereal Disease and the Homosexual," and to the fact that it was published in a journal mainly concerned with venereal diseases. In it, among other things, I analysed the life histories and sexual *mores* of 54 male homosexuals attending a V.D. clinic. My patients differed from those of Dr. Hemphill and his colleagues in that they were free young men-about-town who were contented with their mode of life and were not in any legal or psychiatric trouble. The only significant difference between their findings and mine seems to be that my patients were attracted to adult or adolescent consorts and were not interested in having sexual relations with small boys.—I am, etc.,

London, W.2. F. J. G. JEFFERISS.

REFERENCE

[1] Jefferiss, F. J. G., *Brit. J. vener. Dis.*, 1956, 32, 17.

Occupational Diseases of Musicians

SIR,—In reply to the letter by Dr. M. Anderson (*Journal*, July 5, p. 51) and for the information of others who may be interested, there is a good deal of literature on the occupational diseases of musicians. There is indeed a monograph by Kurt Singer, who was both a specialist in neurology and the music critic for the *Berlin Vorwärts* and who lectured regularly at the Academy of Music in Berlin on the diseases of professional musicians. This was translated from the German by Vladimir Lakond and published by Greenberg in New York in 1932 with the title "Diseases of the Musical Profession: A Systematic Presentation of Their Causes, Symptoms, and Methods of Treatment." There are also numerous articles, the references for which can be obtained from the *Index-Catalogue of the Surgeon-General's Library* and from the *Quarterly Cumulative Index Medicus*.—I am, etc.,

London, N.W.1. F. N. L. POYNTER.

Iatrogenic Disease

SIR,—Your issue of June 21 opens with an article by Dr. John W. Dundee entitled "Iatrogenic Disease and Anaesthesia (*Journal*, June 21, p. 1433). I supposed that I was to read of asthma, say, or rheumatoid arthritis or some other disease that by its length and refractoriness provides sustenance for honest doctors, for iatrogenic means "doctor-begetting," just as carcinogenic means "cancer-begetting," and erogenic "love-begetting." But the learned author defines his word as a malady or an abnormal state produced by physicians. A similar mistake, for such I suppose it to be, is made with the word psychogenic, which means "soul-begetting," not "soul-begotten," as usually intended. I suggest that the word γεννητός (gennētos) is the right suffix, meaning "begotten of"—for example, "Among those born of women (ἐν γεννητοῖς γυναικῶν) there hath not risen a greater than John the Baptist."

For a disease, then, born of a doctor we may write iatrogennete, but we should not write iatrogenic nor yet iatrogenetic.—I am, etc.,

Orpington, Kent. H. ST. H. VERITIE.

Mortality and Morbidity of Steroid Therapy

SIR,—Dr. Michael Kelly in his letter to you (*Journal*, July 5, p. 50) condemns steroid therapy for arthritis, and to prove his case quotes a number of references, including one from myself. I am misquoted as reporting 6 deaths in 90 patients as due to steroid therapy, whereas I commented that one death followed a car accident and two were from carcinoma. One wonders whether his other references are equally inaccurate.—I am, etc.,

London, S.W.1. OSWALD SAVAGE.

Alfred Russel Wallace

SIR,—Dr. F. N. L. Poynter's article on the centenary of the Darwin–Wallace paper on natural selection (*Journal*, June 28, p. 1538) appeals to me, as I have always been an admirer of these two. The following is a note of a visit I made to Alfred Russel Wallace on March 1, 1905.

While doing a locum at Broadstone I was called to the house to see a servant. Asked Mrs. Wallace if they did not once live

at Dorking, my native town. She said Yes, spoke to me of Dorking people, and said her husband would like to hear of them. Mrs. W. took me into the study and introduced me to the professor. He is a tall thin man with snow white hair and beard; stoops very much; wore a very loosely fitting brown suit, thick soled black shoes.

A. R. W. first asked me about people he had known at Dorking and then got on to the subject of his various residences. Dorking did not suit them, it is too much in a valley. He moved to Croydon, then to Godalming, where they lived nine years, then to Parkstone, now in Broadstone. He hunted all along the Downs from Sevenoaks to Guildford without finding a suitable site for a house, or a house with a proper garden. The present house bears the initials A. R. W.; it is on a slight elevation, looks over moorland to Poole and Poole harbour about three miles off. There is a large clump of fir trees in the garden with a small plot of grass; in front of the house is an acre or two of uncultivated moor. Tea was brought in at this stage (about 4 p.m.). Two cups in the ordinary style for Mrs. W. and myself with cake and bread and butter. A. R. W. had a brew to himself: a little tea and much water straight from a kettle over a spirit lamp, poured off almost directly, cup half-filled with milk, sugar two lumps in a small cup, soon disposed of; another cup, less tea this time, more milk, still sugar two lumps; then more cups with less tea each time, still sugar two lumps.

On my rising to go A. R. W. said he must first show me his blue water-lilies, which he said I had never seen before and probably never would again. We went through the greenhouse and here I had the misfortune to knock over a flowerpot and break it. Happily the plant did not appear injured nor the earth shaken from the roots. A. R. W. made light of it, but I was very much annoyed at my clumsiness and could not enjoy the rest of the interview. The blue lilies are very pretty and have an agreeable scent, they come from Port Elizabeth. He showed me a New Zealand plant grown from seed which had not got accustomed to the seasons and flowered in winter. A. R. W. was very chatty and communicative, and if it had not been for the flowerpot incident I should have enjoyed the whole interview very much.

—I am, etc.,

CHARLES A. MARSH.

Bath.

Alcohol and Driving

SIR,—Dr. R. P. W. Kup (*Journal*, July 5, p. 46) writes: "It would appear fairly logical that people [charged with driving under the influence] with a good defence should resort to such a tactic [electing trial by jury] and those without a reasonable answer to the charge should content themselves with a magistrates' court. . . ." In actual fact, it is the other way round. It speaks volumes that the Recorder of London, Sir Gerald Dodson, is reported in *The Times* of May 22 as having said in the Central Criminal Court on the previous day: "I think everyone would welcome a short Act of Parliament which would deprive drivers accused of being under the influence of drink of the right to be tried by a jury."—I am, etc.,

Isleworth, Middlesex.

H. PULLAR-STRECKER.

1959 Medical Directory

SIR,—The annual schedule, upon the return of which the accuracy of the *Medical Directory* depends, has recently been posted to all traceable members of the medical profession, and its speedy return would be appreciated.

A number of schedules, sent to a doctor's last known address, have been returned through the Post Office marked "Gone away." Although in such cases every effort is made to find a new address, I should like to remind practitioners that, if these efforts are not successful before the book goes to press, the names in question will be omitted from the next edition. Any doctor who has not received the annual schedule, or who has mislaid it and would like a duplicate, is requested to communicate as soon as possible with the Editor, *The Medical Directory*, 104, Gloucester Place, London, W.1. The full name and year of qualification of the doctor should be sent for identification, please.—I am, etc.,

B. STANTON,
Editor,
The Medical Directory.

London, W.1.

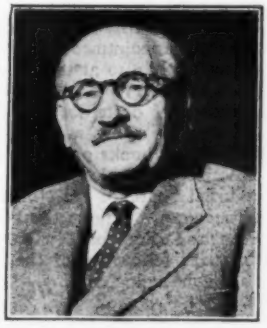
E

Obituary

ANDRIJA STAMPAR, M.D.

Professor A. Stampar, professor of public health and social medicine at the University of Zagreb and President of the First World Health Assembly in 1948, died on June 26, aged 69.

Andrija Stampar was born on October 1, 1888, in Croatia. He studied medicine at the University of Vienna, graduating in 1911. During the first world war he was interned for four years during the occupation of Serbia, but by the time the new state of Yugoslavia had come into existence he had already made a name for himself in the field of public health and preventive medicine. He was only 31 when he was appointed director of public health in Yugoslavia. In the following years he created the public health services of his country, including a network of health centres covering the remoter areas. In 1931 he was elected professor of hygiene and social medicine in Zagreb University and later he became rector of the university and dean of the medical faculty.



For many years he had been one of the most forceful and effective teachers of public health and social medicine, and at the First World Conference on Medical Education, held under the auspices of the World Medical Association in London in 1953, Professor Stampar, as a vice-president of the Congress, took the chair at the meetings of the section which was concerned with preventive and social medicine. Thanks to his outstanding knowledge of the subject, the meetings of that section were particularly successful.

M. D. M. writes: The death of Professor Andrija Stampar will be a deep sorrow to his many friends all over the world. He will be remembered chiefly for the immense contributions he made to international preventive medicine. He began this work in 1924, and until the outbreak of the last war he was continually associated with the activities of the Health Section of the League of Nations, in the countries of Europe, the Americas, Asia, and the U.S.S.R. After the war Stampar again took up his post at Zagreb University, but devoted a steadily increasing part of his time to the development of international medicine, particularly to the creation and functions of the World Health Organization. In 1946 he was elected first vice-president of the Economic and Social Council of the United Nations. After contributing enthusiastically to the work of the Preparatory Committee for the creation of the World Health Organization he was elected as permanent chairman of the Interim Commission which was authorized to assume the responsibilities of the future World Health Organization. In 1948 he became president of the first World Health Assembly in Geneva. Subsequently, for nearly 10 years he headed the Yugoslav Delegation to W.H.O. Stampar's knowledge covered every branch of preventive and social medicine, but he was particularly interested in rural hygiene, the training of doctors and health workers both in their own countries and abroad, and schools of hygiene. Whilst his outstanding career and his wide knowledge called for the admiration of all who met him, it was his dynamic and lovable personality that made him friends everywhere. He was essentially human, and with a keen sense of humour always ready to help in health problems either national or personal. Stampar was twice

married. He had a large family, several of whom continued to live under his roof in the patriarchal system. His very happy family life was a fitting background to the great contribution he made to the progress of mankind, towards closer collaboration in medicine, and a better understanding between nations.

ISIDOR C. RUBIN, M.D., F.A.C.S., Hon.F.R.C.O.G.

Dr. Isidor Rubin, who had an international reputation in gynaecology, died in London on July 10 during a visit from the U.S.A. He was a pioneer in the invention and development of apparatus for insufflation of the Fallopian tubes.

Isidor Clinton Rubin was born on January 8, 1883, and received his early education in New York. After taking the M.D. of Columbia University in 1905, he became an intern at the Mount Sinai Hospital, New York, remaining there until 1909, where he spent a year visiting Vienna, Berlin, and Paris. On his return to the U.S.A., in 1910, he obtained appointments at the Beth Israel Hospital, and subsequently also at the Mount Sinai and Montefiore Hospitals in New York. From 1937 to 1947 Rubin was clinical professor of obstetrics and gynaecology at Columbia University. Not only was Rubin the author of many papers and several books on his specialty, but he undertook many editorial tasks also; these included membership of the editorial board of the *American Journal of Obstetrics and Gynecology*. Among the honours bestowed on him is the French Legion of Honour and, in Great Britain, the honorary fellowship of the Royal College of Obstetricians and Gynaecologists.

Mr. V. B. GREEN-ARMYTAGE writes: Thirty-three years ago in America those on higher gynaecological study leave were attracted by three outstanding men—Whitbridge Williams, John Sampson, and Isidor Rubin, though hardly less so perhaps by Graves of Boston, Curtis of Chicago, and Masson of the Mayo's. Although hysterosalpingography was already on the map, first in Buenos Aires, and later in Paris, Rubin came straight into the limelight when, after many experiments, he discovered that CO_2 was the ideal gas and method for demonstrating tubal patency, and more particularly when he was able to prove that, in the case of the hitherto long-infertile woman, 18% of those insufflated for the first time conceived within the next few weeks. In 1925 this was indeed hot news. In those days his instrument was not his latest minute compact aluminium one, with a graph rotated by electricity and CO_2 activated by a tablet of "alka seltzer," but a heavy, cumbrous, temperamental affair of cylinders, drums, and tubing run by whirring clockwork. Nevertheless it worked, showing normal oscillations or the rises in pressure due to treatable spasm or organic obstruction.

He was generosity itself to postgraduates, and I recall many a visit to his multi-cubicled office in Park Avenue, where we would listen to him, surrounded by nurses, practitioners, and stenographers, as he passed from patient to patient. In those days he was rosy cheeked with rippling auburn hair. He never got rattled; he was always quiet and efficient as he taught us how to work his beloved machine. So impressed was I that, on return to London after many months in the States, I sought out my old friend Clifford White, who was then secretary of the Obstetric Section of the Royal Society of Medicine, and begged him to obtain the ukase to invite Dr. Rubin to give us a paper, whilst I would make myself responsible for his entertainment at the old East India United Services Club. He came, he conquered. His address that October night in 1925 was a triumph. Indeed, with his Heath-Robinson-like apparatus sprawling over the table, he gave us the very first exposition of this technique in Europe. Everything went perfectly, and no one was more thankful than he and I that in a packed Barnes Hall he was even able to convince some of the old diehards of our specialty who were present. This test, by virtue of its proved diagnostic and therapeutic value, made him a benefactor to all mankind. What wonder then that his own great country and every civilized land has praised and honoured him. France at once made him a Chevalier, and then a few years ago promoted him to be an Officer of the Legion of Honour. In Great Britain our own Royal College made him an Honorary Fellow. But though the flame of his fame burned brightly, and his apparatus was acclaimed the world over, the man himself, the real scientific Rubin, remained ever the same, whether on hospital rounds, in operating theatre, or as a friend met casually or by intent in many of the great cities of the world—calm, humble, humorous, and helpful. Indeed, for him and his charming family life was lovely and pleasant. He had friends in every capital. The younger generation never looked in vain to him for help and guidance: I recall him quoting to a group of them at a clinical meeting those words from Masefield's "Adventurer":

> Adventure on, for from the littlest cue
> The next to lighten all men, may be you.

Rubin was always welcomed wherever he went. No better living evidence of the high regard in which he and his work was held can be given than the fact that in 1947 111 of his friends, associates, and pupils presented him with a *Festschrift* to which each of them had contributed a special article. If the measure of any man's greatness is the number of disciples he has gained, or the number of persons of all nations he has helped along the ladder of life to greater happiness, then assuredly Isidor Rubin is among the blessed.

Mr. ELLIOT PHILIPP writes: When six weeks or so ago the University of Mexico City awarded several honorary doctorates, it was for one man alone that the whole audience rose to give a warm spontaneous standing ovation. That man was Isidor Clinton Rubin; and the ovation was a measure of the honour, esteem, and affection felt for him in academic and medical circles throughout both the Americas.

It is not given to many men to make even one worthwhile advance in the knowledge of their specialty, but Rubin made several. His first paper was published in 1910 and shows that already, half a century ago, he was concerned with the early diagnosis of cervical carcinoma and the condition we now call carcinoma in situ. It is worth while quoting the last sentence of this first paper: "The important criteria of malignancy in these early cases lie not so much in the relation of the cell nests to the stroma, the depth or extent of epithelial invasion, or evidences of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

The young man in his twenties had laid a stone in the foundations of the increasingly exact science of early cancer detection. More than that he would himself not claim, although repeatedly his early and his late papers deal with cancer cell detection.

Yet although Rubin had the gifts of a scientific research worker he also had great dexterity as an operator, and a wonderful gentleness and warmth of character that drew people to him. So inevitably he was taken from the laboratory to the clinical field and there became acutely aware of the misery of sterility. With determination and with a band of faithful collaborators at the Beth Israel and Mount Sinai Hospitals in New York he set to work to unravel one problem after another. He did not casually stumble on his discovery that the ovum was conveyed to the uterus by the peristaltic waves of the Fallopian tube. Originally he injected radio-opaque substances into port-mortem specimens, then into a live dog, and in 1914 he carried out the first hysterosalpingography on a patient. In 1919 he was the first person bravely and against the advice of his colleagues (who feared the patient would die of peritonitis) to insufflate the tubes with a gas. He used oxygen and, very soon after, carbon dioxide, which he rightly judged to be safer. This first patient became pregnant shortly afterwards.

He had a severely logical mind and he deduced from his observation of his early insufflation patients that shoulder

pain was diagnostic of stretching the ligaments on the under surface of the diaphragm. Thus he was the first to describe shoulder pain as being of diagnostic value in ruptured ectopic pregnancy.

In his more than fifty years of practice Rubin approached each patient as a human and a scientific problem. He was quiet, gentle, wise, and immensely generous. Above all he was inspiring, yet he detested bombast, hypocrisy and lack of truth, and would not hesitate to criticize a work that he judged prematurely published or inadequately proved.

His consulting-room was adorned by honorary diplomas and fellowships from universities and colleges throughout the world, and two he valued highly were from the University of Paris and from our own Royal College of Obstetricians and Gynaecologists. His high rank in the French Legion of Honour he, too, wore proudly when in France.

His aristocratic and noble patients who came from all over the world to see him adored him, but much more touching was the attention he gave the poor. I took him out to Romford on his only free time—a Sunday morning—last year to see the wards and one or two patients who were either particularly interesting or worrying, but it was at the bed of a woman dying of inoperable carcinoma that he stopped longest to speak words of encouragement. As he left the ward the orderly who had brought him tea said, "That is the finest gentleman I have ever met." And so he was.

To his wife Sylvia, who for so many long years so devotedly encouraged, protected, and helped him, both in his beautifully traditionally orthodox Jewish home and on his world-wide travels, and to his daughters and son, our deepest sympathy goes out. For their love is ours too.

E. L. ELLIOTT, M.B.E., M.B., B.S.

Dr. E. L. Elliott died suddenly after a long illness at his home at Stokenchurch on June 4. He had been in general practice in the district for nearly forty years.

Edgar Lionel (Jack) Elliott, the son of a doctor, was born at Bromsgrove on October 24, 1885. Educated at Marlborough and Guy's Hospital, he graduated M.B., B.S. in 1910, and for a time thereafterwards was house-physician to Sir William Hale-White. From 1914–19 he served as surgeon lieutenant in the Royal Navy, mainly in the Mediterranean theatre in H.M.S. *Somali* and *Karapara*. After the war he entered general practice at Stokenchurch, joining, and later succeeding, his father. In his younger days he had been a keen sportsman, playing Rugby football and cricket with some success at Guy's; after the war riding and hunting became his main hobbies, and he was a familiar figure visiting remote parts of his practice on horseback. A serious accident in 1931 in which he fractured his spine curtailed his riding, and afterwards he became interested in dinghy sailing. He bought a small cottage on the Dorset coast at Ringstead Bay and spent most of his holidays there. During the second world war he was area medical officer to the Home Guard and was awarded the M.B.E. for his services. He continued in active practice after the war in spite of gradually increasing cardiac failure, resulting from valvular disease and aggravated by Paget's disease. Although the prolonged inactivity of his first long illness was irksome to him, he bore it with great patience and good humour.

Dr. Elliott married Miss Mabel Drew Hobley at Sevenoaks in 1912, and she survives him with one son, one daughter, and one adopted son. Both his sons had joined him in his practice.

C. S. writes: E. L. Elliott had been "The Doctor" at Stokenchurch since 1919. In the tradition of his calling he was much more than just a medical practitioner: the parish council, the village sports clubs, the British Legion, the schools, and many other local organizations had known and valued his wisdom and support. To the ordinary people of the villages and hamlets around Stokenchurch he was "their doctor," a man of vigorous habits and cheerful countenance, a wise and humane man, a man who would be very gentle with children and very kind to those in distress. His main interests were in his home and family, in his practice, and, of course, in the fortunes of Marlborough and Guy's.

When he succeeded his father in Stokenchurch he was single-handed, but he had a dynamic personality, and in time his practice grew and he was able to found a group practice. As senior partner and "elder statesman" of the firm for twenty years he was an unfailing source of help and encouragement to those who came to work with him. He believed profoundly in the continuing education of general practitioners, and in breaking down the isolation which had often been the lot of the country doctor in the past. A small local society, known as the XX Club and composed of G.P.s from neighbouring practices, owes much to his influence. All those who have attended the XX Club meetings, whether as members or guests, will know how well worth-while such societies are, and will remember Jack Elliott with deep gratitude. They will also wish to extend their deep sympathy to his wife and family.

H. H. BAYLEY, M.D.

Dr. Harry Bayley died suddenly from a heart attack on June 14, at his clinic in Barbados. He was 49 years of age.

Harold Haynes Bayley was born in Barbados and educated at Harrison College, Barbados, and New York. At the age of 16 he went to Columbia University, where he studied natural sciences, and at 18 went up to Sydney Sussex, Cambridge, where he achieved the feat of passing his second M.B. and getting an athletic blue in his first year. From Cambridge he went to King's College Hospital, being awarded the Burney Yeo scholarship. He qualified in 1934 and graduated M.B., B.Chir. in 1935. In the same year he returned to Barbados, where he started in general practice. His main interests lay in laboratory work, and at an early stage he established his own laboratory. His practice grew steadily until by 1948 he had been joined in partnership by Dr. A. L. Goddard and had built a finely equipped laboratory and a private clinic of 23 beds, with a good *x*-ray department, operating theatre, and all the facilities of a small hospital.

Harry Bayley had great ability and exceptional energy, and while at Cambridge and at King's College Hospital, where his teachers included Professor R. A. McCance and Dr. R. D. Lawrence, he developed an absorbing interest in biochemistry and clinical pathology. These he felt to be the foundation of scientific medicine, and they were to be his special concern throughout his career. General practice in a small West Indian island seemed to offer little scope at first, but by unremitting hard work and determination he was able to give his patients the type of service one associates with the medical department of an English hospital. In 1948 there was an epidemic in Barbados of severe jaundice, which was believed to be a special form of infectious jaundice peculiar to the island. This stimulated Bayley's love of research, and in an exhaustive investigation he proved the disease to be leptospirosis. For a thesis based on this work he was awarded the degree of M.D. in 1942. Other subjects which interested him and on which he published papers were the "bush-teas" of Barbados, larva migrans, the poisonous scorpion fish, and the Galli-Mainini test, using the local *Bufo marinus* toad. His wide scientific training and keen interest in recent developments in medicine helped him to develop a considerable consulting practice. His colleagues found his opinion always sensible and valuable.

Harry Bayley's enthusiasms were not confined to medicine. Astronomy, music, modern languages, and horticulture filled his brief leisure hours, and he had recently completed a remarkably successful hydroponic garden. His gaiety, high spirits, and warm sympathy for his patients made him much beloved in Barbados and the neighbouring

islands. His death at the height of his powers is a great loss to medicine in Barbados and beyond it.

His wife, Iris Bradshaw, was a great help to him in his practice, undertaking the administration of the clinic and carrying out some of the laboratory work. One of his four daughters is a medical student, and our deepest sympathy goes out to them and his wife in their bereavement..—A. L.

H. C. BELL, M.M., L.R.C.P.&S.I.

Dr. Harry Bell died suddenly on July 4 at his home in Weston-on-Trent, Derbyshire. He was 64.

Henry Cooke Bell was born in Belfast on February 17, 1894, and studied medicine at Queen's University. He interrupted his training to volunteer for military service during the first world war, and spent three years on the Western Front with 110 (Ulster) Field Ambulance, becoming its sergeant-major. For his service he was awarded the Military Medal and the French Médaille Militaire. After qualifying in 1921 he spent two years in practice in the Bahamas. Returning in 1924, he and his wife set up in general practice near Derby. He remained in this practice for the rest of his life, and for most of these 34 years he was also medical officer to the Grove Hospital, Shardlow, and Aston Hall Hospital. St. John Ambulance work always claimed some of his scanty leisure hours and he was in great demand as a lecturer and examiner. In all his work the only standard he accepted was the highest. An honest and sincere man himself, he disliked humbug of any kind. Everyone felt at ease with him because he was always so natural and warm-hearted and they all loved him for it. His death has deprived many people of a wise and kind doctor and very many more of a true friend. He is survived by his wife, Dr. Mary C. Bell, and his younger son, who is an officer in the R.A.M.C. His elder son was killed on the Matterhorn in 1948.

Medical Notes in Parliament

ESCAPE FROM BROADMOOR

Mr. HERBERT MORRISON (Lewisham, South, Lab.) asked the Minister of Health by private notice on July 9 whether he would make a statement about the escape of an inmate from the Broadmoor Institution.

Mr. DEREK WALKER-SMITH: Yes, Sir. I regret to say that Frank Samuel Mitchell escaped from the Broadmoor Institution in the early hours of Tuesday morning. He was in the maximum security block, and consequently occupied a single room with the door locked and the window barred and shuttered. His day clothes had been removed from the room. I understand that he escaped by opening the window shutter with a duplicate key, sawing through the window bars, and climbing 30 yards along a high coping. Subsequently, he climbed the outer wall. At or about 4 a.m. he broke into a house at Wokingham and stole clothes and a car, in which he drove away about an hour later. Shortly before 5.30 a.m. the Institution were informed by the police of the events in Wokingham. An immediate check was made, but since Mitchell had left a dummy in his bed, no patients were observed to be missing. At 7 a.m., when the doors were unlocked, Mitchell's absence was discovered and the police were at once informed. The search for him is being prosecuted vigorously. A full, detailed report is being prepared by the medical superintendent, and should reach the Board of Control to-morrow.

Sounding the Alarm

Mr. MORRISON asked why Mitchell was given a room to himself; why there was, apparently, a material delay in surrounding the asylum after the escape, and indeed after the escape became known; and for an assurance that an inquiry—which, he suggested, might be independent—would be instituted into the escape? Mr. WALKER-SMITH replied that Mitchell was accommodated in the way considered appropriate for the maximum security block in which he was. Regarding the siren, at the time when the institution became aware of the escape, that was to say, at 7 a.m., the staff were acting on the information that Mitchell had made his escape in a stolen car. In those circumstances the medical superintendent considered that it was highly improbable that he would be in the locality, and did not, as the Minister understood, give the immediate signal for the siren because of that circumstance and his desire not to alarm the neighbourhood unnecessarily. Before deciding about an inquiry, Mr. Walker-Smith thought it would be better for him to await the report which the Board of Control is receiving from the medical superintendent.

Mr. R. M. BELL (South Bucks, Con.) asked if the fact that Mitchell returned to the neighbourhood of Broadmoor did not show that the decision not to sound the siren was an unfortunate one? Would not it be better for a standing instruction to be given that the siren should be sounded as soon as an escape was discovered? Could the Minister say whether there was any delay in informing police stations in the surrounding countryside of the escape of this dangerous person? Mr. WALKER-SMITH said that action by the police was a matter for the Home Secretary. With regard to the warning siren, the principle was that it should be operated by the responsible officer on duty "as soon as an escape has been detected"—that being the phraseology of the Scott Henderson Report. With the benefit of hindsight, he thought it obviously right now to say that the judgment was an unfortunate one, because, so far from Mitchell having left the locality in the car, it was subsequently discovered that the car had been abandoned. But that was not to say that the appreciation which was made at the time was not a reasonable one, or might not have been a reasonable one, in the light of the facts as then known to the medical superintendent.

Lieutenant-Colonel M. LIPTON (Brixton, Lab.), as one who lived in the immediate vicinity of Broadmoor, asked the Minister very seriously to bear in mind that there was considerable local misgiving about this episode, which was not the first one of its kind. Would he not now consider that, so far as security precautions were concerned, there was reason for saying that the administration of Broadmoor should be returned to the Home Office? Mr. WALKER-SMITH said he had every understanding and sympathy for local feelings and apprehensions, but thought this matter should be kept in the right perspective. Colonel Lipton spoke of a number of escapes, but this was the first escape—with one relatively minor exception, which was a break-away from a working party—since the publication of the Scott Henderson Report in the summer of 1952; and since action was taken following on the recommendations made therein. The question about the transfer of jurisdiction raised a rather wider issue which he did not wish to enter into now.

Mr. A. R. HURD (Newbury, Con.): Does not this episode raise again the whole question of the desirability and wisdom in keeping dangerous criminal lunatics in a district which is fairly thickly populated? Was it really reasonable that the people of Berkshire should be put in jeopardy by a man who could escape, was determined to escape, and within a few miles and a short time after escaping broke into a house, terrorized people, obtained clothes, stole a car, and was away, and neither the police nor anybody at the Institution had a clue as to where he had gone? Mr. WALKER-SMITH agreed that institutions of that sort, obviously, were not popular or an agreeable feature of any locality. While he had every sympathy with the point of view which Mr. Hurd had expressed he must remind him that Broadmoor had been used for this purpose uninterruptedly since 1863.

Value of Treatment

Mr. ANTHONY GREENWOOD (Rossendale, Lab.) asked if it was not a fact that a substantial number of cures had been affected at Broadmoor, and that that would be less likely

if the inmates were cut off from ordinary contact with their families and people outside? Was the Minister aware that, while they all insisted on the maximum security arrangements, many would regard it as a retrograde step if the institution ceased to be a hospital and reverted once again to control by the Home Office? Mr. WALKER-SMITH said that in all these matters they walked the razor edge between trying to have the maximum security, on the one hand, which was a very proper objective of public policy, and, on the other, ensuring the maximum possible rehabilitation, which, as Mr. Greenwood said, worked very well in a large number of cases. It was along that rather difficult razor edge that they tried to make the best progress they could.

Mr. C. F. H. GOUGH (Horsham, Con.): In view of the information that Mitchell was possessed not only of a skeleton key, but possibly also of some form of saw, could the Minister tell them how often thorough searches were carried out both of the men themselves and of the rooms in which they lived? Mr. WALKER-SMITH said he was awaiting that information, as part of the expected contents of the full and detailed report from the medical superintendent to the Board of Control.

Board of Control Inquiry

Colonel LIPTON (Brixton, Lab.) asked on July 14 what action the Minister would take to improve security precautions at Broadmoor. Mr. WALKER-SMITH said that the Board of Control had decided to hold an inquiry into the recent incident at Broadmoor Institution, and he must await their report. Colonel LIPTON asked for an assurance that this would be a full and independent inquiry, in view of the public misgiving, and if it would take note of the unanimous view of the 230 male nurses and others employed there who had made urgent representations that the Home Office should have some say. Mr. WALKER-SMITH said this would be a full inquiry in the sense that it would take into account all matters that were relevant and constitutionally proper for the Board of Control to inquire into; but he told Mr. A. HURD (Newbury, Con.) that it would not be an independent inquiry in the sense of the Scott Henderson Committee of 1952. It was an inquiry by the Board of Control into this specific incident; obviously a somewhat narrower approach.

Mr. R. PAGET (Northampton, Lab.) asked the Minister to bear in mind the remarkable achievements in cure at Broadmoor. He should not be panicked into making medical treatment impossible at Broadmoor. Mr. WALKER-SMITH said that he had those considerations in mind, as well as security.

PREVENTION OF BRONCHITIS

The Rev. LL. WILLIAMS (Abertillery, Lab.) used a comparison between the number of working days lost through strikes and those lost through bronchitis to point the appeal for greater preventive efforts to minimize the disease that he made in an adjunct debate on July 9.

Heavy Mortality and Industrial Loss

He asserted, on the strength of figures showing that the number of deaths from bronchitis in England and Wales were—1930, 19,125; 1950, 28,257; 1955, 28,793; 1957, 26,930 (provisional)—that Britain had the worst record in the world. The death rate was four times as high as in the Ruhr or industrial Belgium, and about 20 times as high as in the Scandinavian countries. In 1951 there were 26.61 million working days lost as a result of bronchitis, and in 1955–6 the number was 26.87 millions. The days lost through strikes were almost negligible in comparison—1.69 millions in 1951, and 2 millions in 1956. Bronchitis was highly aggravated in the heavy industrial areas. The death rates among males (per 100,000) aged between 45 and 65 in 1953 were—Salford 329, Oldham 294, Dudley 286, Manchester 248, and Wigan 246; which contrasted with Eastbourne 48, Great Yarmouth 68, Southport 82, and Canterbury 86. On the other hand, in Coventry, where most of the industry was modern, the rate was 87. In spite of bronchitis being aggravated by non-industrial factors, such as smoking, the causative role played by industry appeared to be substantial. The three main reasons for this appeared to be atmospheric pollution, dust at work, and overcrowding leading to infection.

Preventive measures were surely called for. There must be more stringent limitations on the discharge of sulphur oxides from power stations and railways. There should be a medical inspectorate under the Ministry of Health to supervise measures against dust in industrial establishments. The factory inspectorate could not possibly perform the function properly. What was needed was an occupational health service. The method of dealing with people who contracted bronchitis was also unsatisfactory. The law did not admit the connexion between exposure to dust at work and the bronchitis that resulted, although this and the accompanying emphysema was more disabling than pneumoconiosis. Much bitterness could be traced to decisions by panels relying on *x*-ray evidence alone.

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) added the suggestion that the Minister should call more effectively for the full support of the general practitioners in a real drive in research.

Research in Progress

Mr. RICHARD THOMPSON, Parliamentary Secretary, Ministry of Health, said the cause of the disease was not yet fully known. There was a large body of research in progress under Government auspices, besides other work being done independently, by the universities and elsewhere, with the co-operation of the general practitioner. A long-term study was being made by the College of General Practitioners, with the support of the Nuffield Provincial Hospitals Trust, and based on the family doctor, who was in an especially good position to realize the extent and effect of bronchitis in daily life. The Medical Research Council had a number of groups at work on different aspects of the problem, directed partly to assessment of health hazards resulting from atmospheric pollution. If a key could be found to the problem of acute bronchitis it would be in prevention. The Clean Air Act came into full operation in June, and although there would be no swift and dramatic result it should ensure in time, with other measures, a diminution of one of the basic causes. On the treatment aspect, antibiotics and physiotherapy had extended the life expectancy of the bronchitic.

Two Recent Developments

Two recent developments in clinical treatment had been the release of a number of sanatorium beds because of the decline in tuberculosis, some of which could be used for patients suffering from chronic bronchitis; and the setting aside on an experimental basis of particular wards that were fully air-conditioned. These were discussed by the Standing Advisory Medical Committee in 1956, which at that time formulated no specific advice. Discussions with senior hospital medical officers showed that the regional boards were doing what they could to provide special facilities. Much more information was needed before the possibility of *x*-ray diagnosis could be turned to the advantage of potential sufferers.

OTHER QUESTIONS IN THE COMMONS

Barber v. Manchester Hospital Board

Mr. LESLIE HALE (Oldham, West, Lab.) on July 14 asked the Minister of Health what was the total cost to public funds of the case of *Barber* v. *Manchester Regional Hospital Board and the Minister of Health*; and to what account this sum was to be charged. Mr. D. WALKER-SMITH: The cost to public funds, apart from any apportionment of the

salaries and expenses of officers of the Ministry and of the Board, was £13,865 18s. 7d.; £6,410 7s. 9d. had been charged to the Ministry of Health Vote, and the remainder—through the accounts of the regional hospital board—to the Vote for the National Health Service.

Mr. HALE asked why, as this had been a decision by the Minister, after protests he had made in the House and by a deputation from the regional hospital board, should they have to pay for the folly of the Minister who had declined to accept the advice given him and pig-headedly insisted on contesting the case until the last minute. Mr. WALKER-SMITH replied that he did not accept Mr. Hale's interpretation. The dismissal was a matter for the regional board, as the employing authority. Mr. Justice Barry found that the termination of employment was wrongful, but nevertheless took effect. He gave a penalty in damages, and that was included in the sum to which he had referred.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said the matter had been given considerable publicity. Why did the Minister decide to dismiss the best advice given him, and to take action? Mr. WALKER-SMITH said the Minister was advised by counsel. He did not suppose that Mr. Hale had never had unsuccessful litigation on behalf of a client.

Mr. HALE asked what steps the Minister had taken to comply with the declaration made against him that, in failing to comply with Clause 16 of the Terms and Conditions of Service, he was in breach of statutory duty; and whether he was aware that Mr. Barber had still not been offered any employment in the Health Service; and what action he proposed to take in this matter.

Mr. WALKER-SMITH said he had asked the Manchester Regional Hospital Board to accept a moral obligation to assist Mr. Barber in obtaining suitable employment if he applied for an advertised vacancy in the usual way. Mr. HALE said he accepted what appeared to be a change of heart. He hoped it meant that the Minister would try to see that this distinguished gynaecologist, who was highly esteemed in the district, was found suitable employment in the Health Service.

Dr. SUMMERSKILL asked if the Minister, in view of the fact that this gynaecologist had been completely exonerated, but that such publicity had been given to the case that he must inevitably be prejudiced in the eyes of certain authorities, would underake in the event of his not being accepted for any advertised post in the near future to take a personal interest in the matter and see that the man was placed. Mr. WALKER-SMITH replied that he had not the power. He was governed by the regulations under Section 14(2) of the 1946 Act. They were explicit that vacancies had to be advertised, and appointments could only follow if the appropriate procedure had been taken. No doubt the hospital board would be mindful of the fact that this was a moral obligation case, and could pass that on to other employing authorities.

Dame IRENE WARD (Tynemouth, Con.) said she was not at all satisfied about the moral obligation business. Up to the moment it had worked most unsatisfactorily. It had taken about seven months to get the Minister into consultation with the B.M.A. Could she have an assurance that this moral obligation would be something that really mattered? Mr. WALKER-SMITH replied that she was wrong. The moral obligation procedure had worked well, as could be seen from the fact that there was only a small residual hard core of cases in which employing authorities had as yet found it impossible to provide suitable employment. These were in the main cases where the person concerned was practising in a specialty which had run down.

Royal Commission

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked whether the Royal Commission on Doctors' and Dentists' Remuneration had finished taking evidence; and when the Minister expected to receive their report. Mr. WALKER-SMITH said the process of taking evidence and collecting necessary information would not be completed for some months, and, while the Commission intended to submit their report as quickly as possible thereafter, they did not expect to be able to do so until next year.

Insurance of Cars Towed Away

Mr. C. A. HOWELL (Perry Barr, Lab.) asked the Home Secretary on July 4 what arrangements the Metropolitan Police had made for insurance cover to be provided where police officers in the force remove vehicles under the provision of the Road Traffic Act, 1957, without the owner's consent.

Mr. R. A. BUTLER.—None. Such vehicles when driven by the Metropolitan Police were regarded as vehicles driven for police purposes, and liability for any loss or damage where the police driver was at fault would be accepted as in the case of a police vehicle.

Psychiatric Day Centres

Mr. K. ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on July 7 how many psychiatric day hospitals were in operation; and how many of these were outside the four metropolitan regions. Mr. WALKER-SMITH said there were 25 day centres providing psychiatric treatment; 17 were outside the metropolitan regions. Mr. ROBINSON.—Does the Minister not agree that the day hospital is no longer experimental but a proved method of cure of patients? Would he do all he could to encourage the development of the day hospital? Mr. WALKER-SMITH replied Yes. He certainly welcomed any measure which could reduce the burden of in-patient treatment. The actual provision was a matter for regional hospital boards.

Coronary Thrombosis in Doctors

Mr. A. WOODBURN (Clackmannan and Stirling, East, Lab.) asked the Secretary of State for Scotland on July 8 to what extent a higher proportion of doctors than of the general population die of coronary thrombosis; and what counsel his advisory council had to offer as to the reason. Mr. MACLAY said that according to figures published by the Registrar-General in 1955 the occupational group which included male doctors had a mortality rate from coronary thrombosis 73% above the average for all males over 15. Research was in progress on a number of projects recommended by the Advisory Council on Medical Research on the general problem of coronary heart disease and methods for its prevention and cure.

Mr. WOODBURN asked if Mr. Maclay was aware that this research was greatly handicapped by the fact that it did not have a great deal of co-operation from the individual doctors in getting proper statistics, and that it was only in one or two districts in Scotland where this research was being done that there was co-operation. Since doctors themselves were so vitally interested personally, would it not be a good idea to ask for their co-operation, to try to eliminate the cause of the want of it, or to find some way of avoiding it? Mr. MACLAY said he agreed that it was certainly a matter in which the doctors themselves should be interested. He would consider what Mr. Woodburn had said.

Crematoria

Mrs. H. SLATER (Stoke-on-Trent, North, Lab.) asked the Minister of Housing and Local Government to what extent there was a planned development of provision of crematoria.

Mr. J. R. BEVINS, Parliamentary Secretary, said the provision of crematoria was in the first instance the responsibility of local authorities, except in so far as facilities were provided by private companies, but, in considering any application for loan sanction for such a purpose, the Minister had regard to the desirability both of meeting the growing public demand for cremation and of avoiding overlapping facilities.

Carbromal and Bromvaletone

Dr. REGINALD BENNETT (Gosport and Fareham, Con.) asked the Home Secretary on July 9 whether he had received the report of the Poisons Board on the drugs containing carbromal and bromvaletone; and what action he proposed to take on their recommendations. Mr. R. A. BUTLER stated that the Poisons Board at its meeting on June 18 decided that the evidence before it was insufficient to warrant any change in the recommendation made by the board in 1955 that preparations containing carbromal, or carbromal and bromvaletone, should not be controlled under the Poisons Act. He felt bound to accept this recommendation. The Minister of Health proposed, however, at the suggestion of the board, to invite the committee on drug addiction recently set up under the chairmanship of Sir Russell Brain to examine further the risks attending the abuse of such preparations.

Mass Radiography Protection

Sir FRANK MARKHAM (Buckingham, Con.) asked the Minister of Health what new measures had been approved, or were being considered, for the protection of radiographers in mobile mass radiography. Mr. D. WALKER-SMITH replied that certain technical modifications of mass miniature radiography units had recently been decided on in the light of the latest information about protection requirements, and some of these had already been made. The rest, including the provision of mobile screens with a lead equivalent of at least 1 mm. would be made shortly. None of the modifications had been delayed for financial reasons.

Poliomyelitis in Scotland

The Secretary of State for Scotland supplied to Mr. HECTOR HUGHES (Aberdeen, North, Lab.) the following table showing the notifications of poliomyelitis, in the large burghs, and in the counties of Scotland, respectively, and in various age groups, for the past ten years:

	Total Notifications of Poliomyelitis in Scotland: All Ages	Burghs—in Age Groups			Counties—in Age Groups		
		Under 15	15 to 45	Over 45	Under 15	15 to 45	Over 45
1948	138	47	16	—	52	22	1
1949	185	64	20	2	71	26	2
1950	1,112	577	86	5	360	79	5
1951	316	133	39	—	94	46	4
1952	217	83	17	1	91	21	4
1953	368	161	27	2	136	41	1
1954	421	164	40	4	168	44	1
1955	605	333	48	4	168	49	3
1956	278	110	29	—	102	35	2
1957	173	67	26	—	55	24	1

Hinchliffe Report.—The Minister of Health has stated that he will be able to make a statement on the Hinchliffe Committee's Report on Prescribing when his consultations with the B.M.A. and other professional bodies are completed.

Opticians Act.—The Opticians Act received the Royal Assent by commission on July 7.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Professor V. B. Wigglesworth has been re-elected into the Quick Professorship of Biology for a period of three years ending September 30, 1961.

UNIVERSITY OF ST. ANDREWS

The following degrees were conferred on July 1:

M.D.—[1]C. C. Booth, [2]J. M. McKenzie, [1]A. P. M. Forrest, [2]J. O. Forfar.
CH.M.—[2]W. F. Walker.
M.B., CH.B.—[4]P. D. Lee, [2]I. S. Macmillan, [2]D. N. Grant, [2]Ellen C. G. Tarvit, [2]H. Ridehalgh, [2]G. Wray, [2]J. R. E. Edmondson-Jones, J. M. Anderson, G. Asbridge, C. W. Avery, Ann Barber, Beatrice M. Catto, Doreen E. Chambers, H. R. Chandrachud, A. J. W. Clayton, A. R. Cook, Jane M. Cowan, J. N. Cross, D. J. Dallas, A. G. Davies, B. O. Divis, G. Donachie, W. H. G. Douglas, W. A. A. Famuyiwa, A. L. Forrest, W. R. Grundy, Mrs. Valerie L. Gunn, D. M. Hay, M. A. C. Heavens, A. H. Imrie, Y. Kebreth, C. D. G. Lewis, A. H. McAdam, Rita A. McIntyre, G. M. Maclure, W. S. McMurray, R. D. Mathias, Eleanor M. Mowat, W. J. Nicol, D. W. Nisbet, Beryl Y. J. Pay, J. L. Penny, Mrs. Toby T. B. Phillips, P. G. C. Robertson, Veronica M. C. Robinson, L. C. Rose, Mrs. Brigid I. Russell, Natalie A. Sender, Avril J. Smallwood, J. S. Soutar, J. L. Stoller, S. Tabaqchali.

[1]With honours and a Rutherford gold medal. [2]With honours and a University gold medal. [3]With commendation. [4]With honours.

UNIVERSITY OF GLASGOW

The following degrees were conferred on July 5:

M.D.—E. McL. Barbour, J. M. Crawford, *W. S. Foulds, *W. J. Gordon, J. A. McKinnon, *R. M. H. McMinn, *J. T. Naismith, *D. D. Smith, *H. I. Tankel.

M.B., CH.B.—O. da R. Afodu, A. N. Ahmad, W. C. Alston, G. K. K. Asamoah, H. D. Baillie, R. Baird, *A. Ballantyne, Maureen E. Barr, R. F. Barr, Isabelle B. Barrie, W. N. Baxter, B. J. Beadsworth, J. Bonnar, *J. H. H. Bowie, Dorothy A. Brown, Jean G. Brownlie, K. D. Buchanan, H. S. Conn, W. G. Conn, N. A. Coutts, J. E. N. Dickie, *Margaret C. Donnelly, A. Downie, B. Drever, J. C. Drever, M. Duncan, J. J. Dunn, J. A. C. Fisher, A. Fleck, S. Fletcher, J. Fyfe, Catherine A. Gardner, Joyce O. Garven, R. T. Glen, R. Gordon, J. Gray, K. D. Griffin, Margaret. E. Hanlon, W. J. Haran, C. D. Hardie, H. C. Hendrie, Margaret Hennigan, D. M. C. Hislop, Margaret A. Hodson, *J. M. Howat, I. M. Hynd, G. M. Irvine, J. F. St. C. Isbister, Irene M. J. Jackson, J. C. Kellock, M. A. Kelly, M. Kelvin, Margaret M. Kennedy, H. A. Kilpatrick, I. McA. Kyles, Marjorie M. Langmuir, J. P. Lanz, I. McA. Ledingham, R. E. M. Lees, D. R. H. Lewis, T. I. McBride, J. P. McConnell, D. M. MacDermid, D. M. Macfadyen, D. B. MacGregor, Eileen McGuire, R. L. McKechnie, M. C. MacKenzie, C. A. MacLean, N. MacLean, R. B. Macleod, G. W. McNicol, Margaret M. Macpherson, J. M. Maguire, J. P. Malone, W. D. Martin, Heather M. May, J. M. B. May, Marie H. H. Mitchell, J. Moffat, J. Murgatroyd, Helen McB. G. Murray, Jean R. Nairn, E. A. Neville, Elizabeth J. Nivison, V. R. Nurse, S. S. I. Parker, K. C. Paton, Mary H. Paul, *P. H. Pinkerton, A. Pollock, J. G. Pollock, Janet S. Primrose, A. J. Quigley, A. A. Reid, D. Reid, G. L. I. Reilly, Elizabeth M. Riddell, *R. L. Robinson, A. Rourke, Elizabeth M. Russell, J. L. Russell, R. Scott, W. S. Scott, M. S. Seltzer, M. G. Sharman, G. R. Sharp, W. Simpson, J. F. Smart, D. Smith, K. Sorooshian, J. C. Spence, A. R. Stewart, T. McC. Stewart, W. B. Stewart, Sheila M. Strachan, *J. P. Studzinski, Morag C. Thomson, *J. K. Todd, Maelor Vallance, A. Vost, Evelyn McD. Walker, *F. Walker, J. P. Wall, J. M. Walsh, R. A. Willett, Maureen L. Wyllie, H. N. Young.

*With commendation.

UNIVERSITY OF ABERDEEN

The following degrees were conferred on July 3:

M.D.—I. R. Lawson, W. G. D. Murray, C. H. Walker.
CH.M.—*With honours*: William Burnett.
M.B., CH.B.—Kathleen M. R. Chrystal and J. A. Baldwin (both with honours), G. A. German and D. G. Jamieson (both with commendation), Elizabeth A. Abernethy, J. E. Ashun, Eileen M. Beattie, A. W. S. Brown, R. N. Carter, Anne M. Cluness, J. T. Coull, J. I. Coutts, J. A. Craig, Noreen M. Crookshanks, G. Dilion, Carol M. Edmond, W. J. W. Freeland, G. A. T. Gill, R. W. Glashan, D. R. Grieve, E. H. Innes, F. K. A. Laing, J. E. Leng, J. G. Lillie, W. S. P. McGregor, J. S. McIntosh, Helen R. McKilligin, R. M. MacLachlan, Sheila C. Martin, Catherine K. Masson, Moira S. Meldrum, A. P. Mowat, A. P. Nicholson, A. G. Nicol, P. P. S. Nylander, J. Proudfoot, R. L. Pyle, W. D. Pyle, Jean McC. Ritchie, G. S. Robertson, R. J. Robertson, Isabelle M. Roe, H. J. M. Spicer, G. A. Taylor, J. Taylor, R. A. Tozer, Grace C. Turner, A. C. Watt, Jean A. Wright, R. A. Wynter.

Diplomas have been granted as follows:

D.P.H.—A. G. Beattie, R. F. Blackburn, Fiona J. Lyall (née Fraser), D. M. McLellan, N. Marshall, T. F. Rennie.

The following prizes and medals have been awarded: *Anderson Gold Medal and Prize in Clinical Medicine, Keith Gold Medal in Surgery, MacQuibban Prize in Medicine, Murray Medal and Scholarship for the most distinguished graduate in medicine of session 1957–8,* and *Davidson Smith Prize in Diseases of Children,* Kathleen M. R. Chrystal. *Alexander Smith Cardno Prize in Anatomy* and *Silberg Prize in Anatomy,* W. G. Skene. *Cash Medal for M.D. thesis (1957),* D. W. Taylor. *Chanock Gold Medal in Anatomy* and *Lizars Gold Medal in Anatomy,* J. M. Leegaard. *Matthews Duncan Gold Medal in Obstetrics,* G. A. German. *Durno Prize in Anatomy,* Mrs. Anne Chew. *Fife Jamieson Gold Medal in Anatomy,* Mrs. Anne Chew and D. Stenhouse (equal). *MacQuibban Prize in Surgery,* D. G. Jamieson. *Ogston Prize in Surgery,* S. D. Preston. *Shepherd Memorial Gold Medal in Surgery,* J. A. Baldwin. *John A. Watt Prize in Preventive Medicine,* W. D. McKay.

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

At a recent examination the following medical practitioners were awarded the Diploma in Gynaecology and Obstetrics:

F. C. Das, Gauri Deb, Azima I. Qureshi, Sarah Ramachandran, I. Raychaudhuri, S. Sarkar.

The following degrees were conferred on July 3:

M.D.—T. H. Bewley, F. O. Dosekun, Edna La C. Murphy.
M.A.O.—C. J. B. Orr.
M.B., B.CH., B.A.O.—Sara R. Abels, Bridget M. Acheson, H. B. Allen, J. Bennett, P. J. Blackburn, J. S. Brown, R. J. M. Collis, Edith M. Cross,

N. J. B. De Wet, Bridget A. M. Dunne, M. Elder, B. Gallagher, P. B. Galvin, H. G. Grace, Sheila D. Graham, D. E. Jones, Anne Llewellyn, S. H. M. Logan, Patricia M. Norman, J. Quinn, Joan Richards, Annette L. K. Roberts, P. J. Robinson, W. M. Robinson, Lorna J. Rust, Pauline E. Tan, D. G. Weir, T. D. H. Wilson, T. Winston, Susan E. J. Young.

UNIVERSITY OF MANCHESTER

The following candidates have satisfied the examiners at the examination indicated:

FINAL M.B., CH.B.—J. W. Aspinall, R. Battye, F. H. Brindle, D. B. Brookes, J. E. Brooks, A. L. Buckley, E. Charles, P. J. Cox, J. S. Cumming, B. Deakin, B. H. Delany, G. G. Duckworth, R. M. Flinn, Joyce Harris, R. Haworth, Patricia A. Hegarty, R. Holmes, A. Hopkins, W. H. Isbister, Maria Z. Kozubowska, R. J. Lawton, I. P. McEwan, A. C. Peterson, J. D. Rhodes, P. H. Roberts, M. Ryan, Elizabeth M. Spencer, R. Statham, Garo Tahta, P. Watson, J. M. Watts, B. K. Wignall, J. D. G. Williams, S. K. Wood, P. B. Wrigglesworth.

UNIVERSITY OF LEEDS

The following candidates have been approved at the examinations indicated:

M.B., CH.B.—Margaret Barber, Pauline Bittiner, N. Carr, F. Carter, Margaret E. Coles, A. J. K. Dore, M. W. Flowers, Gillian M. Foster, R. D. Jackson, J. N. Lambton, P. B. Pickles, S. Sorkin, Freda M. Tomlinson, B. K. Turnbull, R. K. Wright.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—J. Blackburn, Margaret W. Galley, *Mary Jones, H. B. Kidd, *J. T. Rose, B. Ward.

*With distinction.

UNIVERSITY OF SHEFFIELD

Dr. Suzanne K. R. Clarke has resigned her appointment as Lecturer in Bacteriology and Virus Diseases.

UNIVERSITY OF BRISTOL

H. M. Leather and H. Urich have been approved at the examination for the degree of M.D.

The following candidates have been approved at the examination indicated:

M.B., CH.B.—[1]R. T. Marcus, [1]M. Nicholas, [1]R. A. Sharpe, R. A. R. Abraham, Daphne M. Allen, Sarah M. Brewer, Barbara A. Brooking, J. Brunning, R. A. Bunting, J. B. Burchill, M. Busson, Joan R. Coombs, T. O. Dada, P. Dent, S. V. C. Egonu, C. C. Entwistle, P. T. Gardner, R. A. G. Huish, G. H. Hulands, F. W. Lewis, Susi G. Leyton, Alison J. McConnell, B. S. Milner, C. D. Murphy, E. O. Olurin, Glenys R. Packer, M. LeM. Parker, A. P. C. H. Roome, M. H. Saunders, E. J. Seymour, F. D. Skerrett, J. M. Slater, [2]I. Surveyor, L. H. Thean, U. Viswalingam, J. T. Ward, Juliet M. Whitehead, Mary G. Wilmot. *In Group I, completing the examination:* Yvonne E. J. Marot, V. P. Nagpal, M. P. Patel. *In Group I, only:* Anne P. Simon. *In Group II, only:* A. H. Ogden, Glennys S. Shute.

[1]With second-class honours. [2]With distinction in public health.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on June 12, with Sir James Paterson Ross, President, in the chair, a resolution of condolence was passed on the death of Lord Webb-Johnson, past President of the College.

The Hallett Prize was awarded to Miss M. V. Ramchandani, of the University of Bombay.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

On July 4 the following candidates were admitted to the Licence in Medicine and Midwifery of the College:

J. A. Aziz, G. O. Balogun, G. A. Bharmal, N. P. Boyle, D. C. P. Brown, J. J. V. Caraher, F. B. A. Coker, D. P. Connolly, Josephine P. Cummins, D. A. F. Doherty, J. F. Doyle, P. A. Egbe, M. J. Fennell, J. G. A. Fitzgerald, Eithne M. A. Flood, G. Blankson-Hemans, J. T. Hogan, Mary C. Horgan, O. G. L. Hunter, J. H. Jackson, A. M. Jeeva, Mary J. Keating, Mary P. R. Kenny, N. M. N. Lamki, T. Morgan, J. Mullins, J. F. X. McGlade, Ina L. McGregor, P. McLean, P. R. P. Naidu, B. R. O'B. Nation, M. J. Noronha, Catherine O'Connor, E. O'Daly, C. M. Omarjee, R. J. Osborne, Mary Owens, R. Quirke, S. D. Ram, D. F. Reynolds, Dolly T. Salami, S. K. Suleman, D. Svenne, J. B. Swan, W. H. Tweedell, T. R. Vij, P. B. Vilain, F. G. Walls, Lt. A. G. Wharton, L. R. L. Whitelocke, T. A. Worth, P. Zamick.

ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

At a meeting of the General Body of Fellows of the Royal Australasian College of Physicians held in Sydney on June 4, the following were elected and admitted to Fellowship of the College:

Under Article 44: Surgeon Rear-Admiral Lionel Lockwood, of Victoria; Professor J. A. R. Miles, of New Zealand, and Professor J. S. Robertson, of South Australia. *Under Article 42:* Dr. R. A. Bakewell, Dr. J. D. Bergin, Dr. R. C. S. Dick, Dr. W. G. Gray, Dr. G. P. Hallwright, Dr. J. A. Keeling, Dr. L. S. A. Lewis, Dr. R. W. Medlicott, and Dr. C. P. Powles, of New Zealand; Dr. R. B. Blacket, Dr. Clair Isbister, Dr. A. G. McManis, Dr. R. D. Pufiett, Dr. D. S. Stuckey, and Dr. Helen M. Taylor, of New South Wales; Dr. Joseph Bornstein and Dr. H. N. B. Wettenhall, of Victoria; Dr. J. V. Gordon and Dr. B. S. Hetzel, of South Australia; Dr. G. B. V. Murphy and Dr. N. V. Youngman, of Queensland.

The following candidates, who were successful at an examination held in New Zealand, were admitted to Membership of the College on June 3:

Dr. R. J. Cantwell, Dr. T. P. Casey, Dr. R. J. M. Coates, Dr. C. O. Crawford, Dr. P. M. Dennis, Dr. F. E. Dreifuss, Dr. J. D. Frankish, Dr. Colleen A. Hall, Dr. E. E. Hannah, Dr. H. J. H. Hiddlestone, Dr. R. O. H. Irvine, and Dr. Malcolm Watt.

The following candidates, who were successful at an examination held in Australia, were admitted to Membership of the College on June 3:

Dr. L. Bernstein, Dr. R. W. Boden, Dr. G. M. Bourke, Dr. B. S. Clifton, Dr. H. Kronenberg, Dr. L. Lazarus, Dr. M. A. Mishkel, Dr. J. G. Opie, Dr. W. K. A. Paver, Dr. June M. Raine, Dr. F. L. Ritchie, Dr. W. A. Seldon, Dr. N. A. Talley, and Dr. W. H. Wolfenden, of New South Wales; Dr. R. R. Andrew, Dr. P. F. Bladin, Dr. D. M. Danks, Dr. A. P. Dorevitch, Dr. J. A. Game, Dr. G. S. Hale, Dr. A. D. McCutcheon, Dr. F. I. R. Martin, and Dr. S. Shub, of Victoria; Dr. T. H. Beare, Dr. J. R. Lawrence, and Dr. R. H. C. Rischbieth, of South Australia; Dr. J. M. Sutherland, of Queensland; Dr. B. C. Bignold, of Western Australia.

Dr. M. C. Fowler, of South Australia, and Dr. R. D. K. Reye, of New South Wales, were admitted to Membership under the provisions of Article 37.

Medico-Legal

"BROADMOOR PATIENTS"

[FROM AN EXPERT IN FORENSIC PSYCHIATRY]

The escape last week from Broadmoor of Frank Mitchell[1] has focused considerable attention on this unique institution. Comment in the press and elsewhere has reflected, over and above a natural anxiety, some considerable confusion about the function of Broadmoor and the status of its patients. Some factual information about these points may therefore be helpful.

Broadmoor Institution

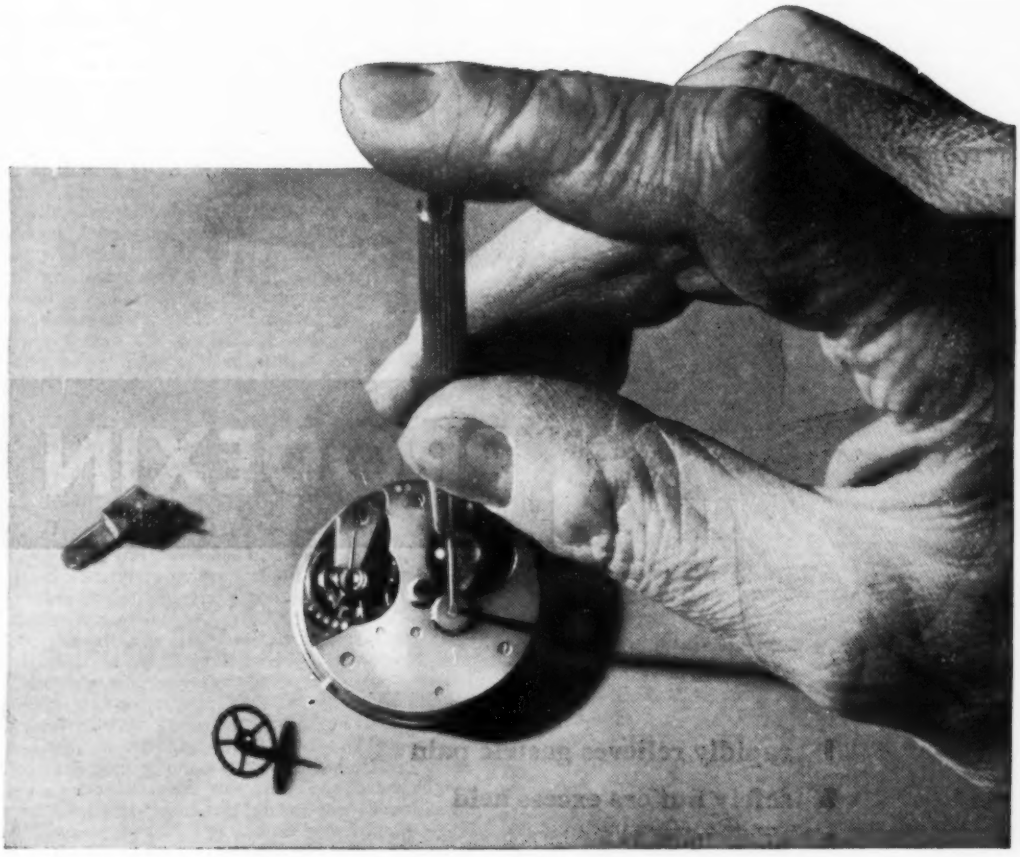
An attempt on the life of George III led to the passing of the Criminal Lunatics Act of 1800, which was to accord recognition to the special position of the insane criminal in law. The King's assailant, Hadfield, was found not guilty on a charge of high treason, "being under the influence of insanity." He was ordered to be detained during His Majesty's pleasure. Eighty years later another attempt was made on the life of the reigning monarch, then Queen Victoria. The assailant was again found to be "Not guilty, being under the influence of insanity." The Sovereign is reported to have retorted, "Insane he may be, but guilty he most certainly is." The following year the Trial of Lunatics Act, 1883, gave official status to the somewhat paradoxical verdict of "Guilty but insane" (see below).

Meanwhile in 1863 Broadmoor Criminal Lunatic Asylum was opened under the provisions of an Act of 1860. Among the first patients admitted was Daniel McNaughton, who earlier had given his name to the historic set of rules governing criminal responsibility.[2] The Criminal Lunatics Act of 1884 modified and amended previous legislation governing the insane criminal and it is under the provisions of this Act and that of 1860 that individuals are detained as Broadmoor patients to-day. The Criminal Justice Act of 1948 provided that Broadmoor Criminal Lunatic Asylum should henceforth be known as Broadmoor Institution, that the expression "criminal lunatic" should cease to be used and should be replaced by that of "Broadmoor patient," that the institution previously run by a council appointed by the Secretary of State should henceforth vest in the Minister of Health and be managed by the Board of Control, and that the employees engaged therein should be deemed to be engaged in health services. Although under this Act the management of Broadmoor Institution and all matters relating to the care and treatment of the patients became the province of the Ministry of Health, none the less the authority to admit or to discharge a Broadmoor patient, whether in the institution or in a mental hospital (see below), remains the prerogative of Her Majesty's Principal Secretaries of State, usually that for the Home Office.

Admission and Discharge

All Broadmoor patients—i.e., those dealt with under the 1860 and 1884 Acts—are not treated in Broadmoor Institution. Of about 1,100 Broadmoor patients at the end of 1956

This man has Parkinsonism



but he also has

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TRIHEXYPHENIDYL

*REGD. TRADEMARK

The classic treatment for postencephalitic, arteriosclerotic and idiopathic Parkinsonism

ELIXIR *2 mg. per 5 cc. Bottles of 16 fl. oz.*
TABLETS *2 mg. and 5 mg. Bottles of 100 and 1,000*

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1 **rapidly relieves gastric pain**
2 **safely buffers excess acid**
3 **non-alkalising**
4 **non-constipating**
5 **stable, consistent and predictable**

Prodexin tablets sucked regularly provide continuous buffering of gastric acid at about *p*H 4, in the face of widely differing acidities and irrespective of the rate of emptying of the stomach. Prodexin does not make the stomach alkaline and does not stimulate compensatory secretion of acid. The tablets are pleasant to take, non-gritty and non-constipating.

PRODEXIN
Each Prodexin tablet contains:
Aluminium glycinate
(dihydroxy aluminium aminoacetate).....0·9 gramme
Light magnesium carbonate.....0·1 gramme

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some 900 were being treated in Broadmoor Institution, the rest in regional mental hospitals. These latter had usually been charged with less grave offences. Three principal groups of persons may be detained as Broadmoor patients by warrant of one of Her Majesty's Principal Secretaries of State. They are: (*a*) Those who can be ordered to be kept in custody during Her Majesty's pleasure. These will comprise those who have been found to be insane on arraignment (and therefore not tried on the charge) and those who have been tried and found to be guilty but insane. (*b*) Any person whom the Secretary of State may order under any Act of Parliament to be removed to a mental hospital. (*c*) Any prisoner who before or after trial is certified to be insane. Prisoners who are certified before their trial are almost invariably produced in Court as soon as their condition enables it to be done without detriment to the dignity of the Court or their own health. Secretary of State patients certified while undergoing prison sentence (Mitchell was one) alone among the whole group stand convicted of any crime. Verdicts of insane on arraignment and guilty but insane are tantamount to ones of acquittal. They do not represent a conviction on the indictment, and there is therefore no right of appeal in such cases.[3]

Rather more than half the annual admissions to Broadmoor Institution are made up of those who had been charged with murder or attempted murder. The rest cover a wide variety of crime—unnatural offences, rape, burglary, forgery, arson, and so on.[4] The psychiatric classification of these patients shows a similar variety and reflects the composition of any psychotic group elsewhere.[5] A number of psychopathic patients are admitted in a psychotic or pseudo-psychotic episode.

Discharge of a Broadmoor patient, whether from a mental hospital or from Broadmoor Institution itself, rests finally with the Secretary of State, usually the Home Secretary, since the decision must take into account not only the immediate interests of the patient but also those of society. Broadmoor patients are not therefore automatically discharged as soon as the formal psychotic symptoms have remitted but only after a prolonged period of observation and abundant evidence of stability. The responsibility for assessing these patients' fitness for discharge and for giving formal authority to discharge them is a very onerous one. Those who have been certified as Broadmoor patients while undergoing a prison sentence must at the conclusion of that sentence be absolutely discharged from the condition of Broadmoor patient and if still insane are detained in a mental hospital as ordinary certified patients. "Pleasure patients"—i.e., the insane on arraignment and the guilty but insane—may also be transferred to an ordinary mental hospital if at a later stage this is deemed appropriate. If suitable, they may also be conditionally discharged to the care of friends or relatives, one of whom must act as guarantor. They may be recalled to the institution if there are any signs of relapse. There is no recorded case of a conditionally discharged murderer committing a second murder. The insane on arraignment are technically liable to be tried on recovering their sanity, but this seems to be extremely rare. The *Report of the Ministry of Health* for 1956[6] shows that at the beginning of the year there were 734 male and 195 female patients in Broadmoor Institution. During the year 74 patients were admitted, 64 males and 10 females; 18 were discharged recovered (17 males and one female) and 37 transferred to other mental hospitals (32 males and 5 females). One case was readmitted on revocation of conditional discharge.

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1 *Manchester Guardian*, July 9.
2 Morton, L. T., *Brit. med. J.*, 1956, **1**, 107.
3 *Archbold's Lunacy and Mental Deficiency*, 1915, p. 711. Butterworth and Co., London.
4 *Criminal Statistics (England and Wales), 1952-1956*. H.M.S.O., London.
5 McGrath, P., *Howard J.*, 1958, **10**, 38.
6 *Report of the Ministry of Health for the Year Ended 31st December, 1956*, Part I. London, H.M.S.O.

Vital Statistics

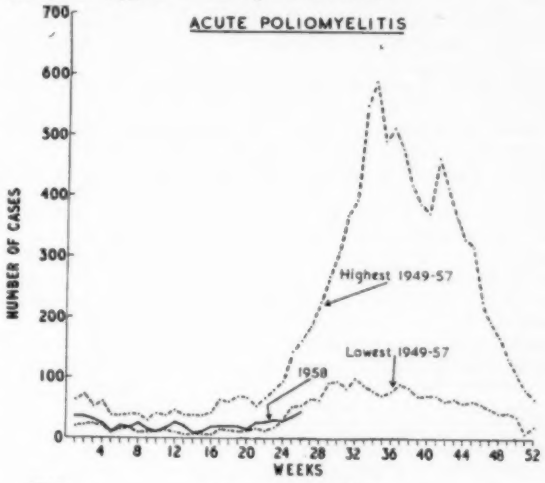
Eire in March Quarter

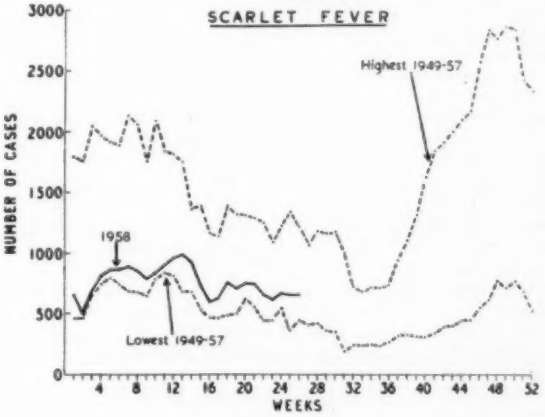
The birth rate for the March quarter of 1958 was 20.1 per 1,000 of the population and was 0.3 below the rate for the first quarter of 1957. The infant mortality rate was 44 per 1,000 registered births, and the neonatal mortality rate was 29; these rates were 6 and 4, respectively, above the rate for the preceding first quarter. The death rate was 14.1 per 1,000 of the population and was 0.7 above the rate for the corresponding quarter of 1957.

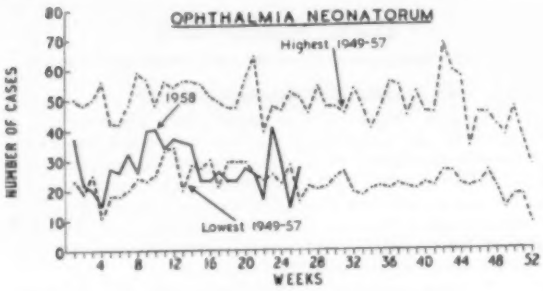
Deaths from respiratory tuberculosis numbered 147 and from other forms of tuberculosis 26, compared with 147 and 33, respectively, for the preceding March quarter. Deaths from infectious diseases included 180 from influenza, 35 from gastro-enteritis (under 2 years of age), 4 from acute poliomyelitis, 3 from diphtheria, and 2 from whooping-cough. Deaths from malignant neoplasms numbered 1,247, and of these 569, or 46%, were due to malignant neoplasms of the digestive system. Of the 273 deaths attributed to all forms of violence 63 were due to motor-vehicle accidents.

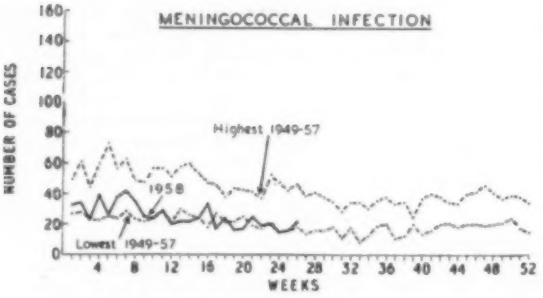
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending July 5

The largest variations in the trends of the notifications of infectious diseases in England and Wales during the week ending July 5 were increases of 412 for measles, from 6,026 to 6,438, 81 for food-poisoning, from 261 to 342, 46 for dysentery, from 873 to 919, and 37 for whooping-cough, from 783 to 820.

The largest rises in the incidence of measles were 188 in Lancashire, from 758 to 946 (Liverpool C.B. 263, Blackburn C.B. 117, Manchester C.B. 99), 71 in Warwickshire, from 191 to 262 (Birmingham C.B. 176), 70 in Cornwall, from 156 to 226 (Falmouth M.B. 85), and 54 in Shropshire, from 88 to 142 (Oakengates U.D. 75); the largest falls were 72 in Derbyshire, from 224 to 152, 59 in Gloucestershire, from 220 to 161, and 52 in Denbighshire, from 102 to 50. The notifications of scarlet fever numbered 663, being 1 more than in the preceding week, and there were no large fluctuations in the local returns. The largest rises in the number of notifications of whooping-cough were 25 in Yorkshire West Riding, from 53 to 78, and 20 in Durham, from 35 to 55. Three cases of diphtheria were notified, being 2 fewer than in the preceding week.

The notifications of acute poliomyelitis numbered 48, and there were 1 more for paralytic and 4 more for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 12 (Halifax C.B. 3, Leeds C.B. 2), Essex 6 (Hornchurch U.D. 2, Rochford R.D. 2), Lancashire 4, Staffordshire 4 (Cheadle R.D. 4), Surrey 4 (Woking U.D. 3).

The chief centres of dysentery were Yorkshire West Riding 202 (Thorne R.D. 54, Barnsley C.B. 23, Leeds C.B. 23, York C.B. 15, Rotherham C.B. 13, Sheffield C.B. 13, Bradford C.B. 10); Lancashire 130 (Liverpool C.B. 22, Manchester C.B. 21, Burnley R.D. 13, Rawtenstall M.B. 10), London 119 (Islington 31, Bermondsey, 14, Finsbury 10), Durham 44 (Whickham U.D. 11, Easington R.D. 11), Berkshire 42 (Easthampstead R.D. 40), Essex 37 (Walthamstow M.B. 24), Staffordshire 37 (Rugeley U.D. 14), Middlesex 36 (Willesden M.B. 12), Gloucestershire 29 (Bristol C.B. 19, Gloucester C.B. 10), Warwickshire 25 (Bedworth U.D. 10), Yorkshire North Riding 25 (Middlesbrough C.B. 22), Hampshire 24 (Droxford R.D. 12, Havant and Waterloo U.D. 11), Surrey 21 (Banstead U.D. 10), and Cambridgeshire 20 (Cambridge M.B. 19).

The largest outbreak of food-poisoning notified during the week was 138 cases in Birmingham C.B.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **June 28** (No. 26) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	5	0	0	0	2	4	0	2	0	2
Dysentery	873	85	136	3	11	464	40	223	8	2
Encephalitis, acute	2	0		0		4	0	0	1	
Enteric fever:										
Typhoid	1	0	0	0	1	3	0	1	0	
Paratyphoid	8	0	0	0		2	1	0	0	1
Food-poisoning	261	36	7	3		228	28	73	0	
Infective enteritis or diarrhoea under 2 years				16	27				23	44
Measles *	6,026	475	104	44	39	17,417	584	121	173	108
Meningococcal infection	22	1	11	2	2	18	3	5	0	2
Ophthalmia neonatorum	27	1	6	0		22	1	8	0	
Pneumonia †	218	12	133	2	1	252	18	123	5	1
Poliomyelitis, acute:										
Paralytic	29	2	} 16	0	7	{ 73	8	} 4	11	1
Non-paralytic	14	2				46	1			
Puerperal fever ‡	170	25	9	1		215	34	6	0	
Scarlet fever	662	44	85	16	17	436	44	59	19	11
Tuberculosis:										
Respiratory	565	66	101	19		553	51	150	24	
Non-respiratory	87	7	11	9		71	8	14	5	
Whooping-cough	783	42	42	29	67	1,554	49	90	5	21

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	1	0		0			0	1	0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	2	0	1	1	1		0	1	0	1
Influenza	11	1	0	0	0		0	0	0	0
Measles		0	0	0	0		0	1	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	313	34	9	8	6		23	11	11	6
Poliomyelitis, acute	0	0		0	0		0		1	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 61	{ 2	6	0	5		5	8	2	4
Non-respiratory		0	0	0	0		0	1	0	2
Whooping-cough	0	0	0	0	0		0	0	0	0
Deaths 0–1 year	287	23	20	9	6		36	27	9	17
Deaths (excluding stillbirths)	8,377	661	532	76	151		690	494	107	145
LIVE BIRTHS	14,107	1314	939	209	383		1157	1017	230	518
STILLBIRTHS	324	21	26				15	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

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PERSONAL ACCIDENT INSURANCE SCHEME

Death *or* Permanent Total Disablement
resulting from accident

10s. per annum *for each* **£1,000** unit
Maximum: 10 units per member = £5 premium: £10,000 cover

UNIT OF BENEFIT

FULL COVER

a **Accidental Death** *occurring within 52 weeks of date of accident* **£1,000**

b **Loss of limbs or sight,** or loss of one limb **and** sight in one eye, *as a result of accident* **£1,000**

c **Permanent total disablement** (as definition below) *as a result of accident* other than as stated in (*b*) above **£1,000**

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Maximum: 10 *units.* **£3 10s. premium: £10,000 cover**

INCOME TAX — The portion of the premium applicable to the fatal accident cover, i.e. 7s. per unit, will, subject to statutory limitations, rank for tax relief. £3 10s. of the total £5 premium for the maximum £10,000 of full cover will thus qualify.

DEFINITION — **Permanent Total Disablement** shall mean a disablement, except for disablement under (*b*), which for 52 consecutive weeks totally prevents an insured member from following any occupation as a registered medical practitioner within the medical profession, and is thereafter declared to be permanent.

N.B.—If necessary a medical referee appointed by the B.M.A. will decide whether or not a disablement is permanent.

AGE LIMIT — Participation in the scheme will cease at renewal date following the 70th birthday.

ADVANTAGES

The cover is particularly wide and includes accidents occurring both in the course of professional duties and other private activities.

The exclusions, stated in full below, have for the majority of practitioners little or no limiting effect, especially so far as professional duties are concerned. Apart from the standard war and suicide exclusions, virtually every activity is covered except private flying, motor-cycling and mountaineering (unless these activities are undertaken in the course of professional duties). Steeplechasing, piloting of an aircraft and riding or driving in any kind of race are *always* excluded.

The period of 52 weeks during which an accident may prove fatal is much longer than usual.

Permanent Total Disablement cover is wider than the normal.

Specially low rate of premium for members of the B.M.A. only.

EXCLUSIONS

Accidental death or disablement due to or arising from:—

(i) Travelling by air other than
  (*a*) as a fare-paying passenger in an aircraft of a regular air line or a Charter air line, or
  (*b*) as a passenger in any aircraft in the course of professional duties.

(ii) Motor-cycling either as a passenger or driver (other than in connection with professional duties); steeplechasing; mountaineering where use of ropes and guides is customary (other than in connection with professional duties), and riding or driving in any kind of race.

(iii) Any consequence of war, invasion, act of foreign enemy, hostilities (whether war be declared or not), civil war, rebellion, revolution, insurrection or military or usurped power. Suicide or attempted suicide (whether felonious or not). Voluntary act of an insured member (other than for humane or professional purposes): venereal disease or alcoholism.

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Please register my name for participation in the B.M.A. Personal Accident Insurance Scheme.

I am a member of the British Medical Association enjoying normal health for my age and do not suffer from any physical infirmity.
(If retired, please state this fact.)

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ADDRESS .....

.....

QUALIFICATIONS.....

Signature..... TEL. NO..... *Date*.....

NUMBER OF UNITS

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DATE OF BIRTH

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4/7

B.M.A. PERSONAL ACCIDENT INSURANCE SCHEME . . .

The Council of the British Medical Association has become increasingly aware of the need of its members for suitable provision against the risk of accidental death or permanent total disablement arising from accident, which would prevent them from carrying on their profession.

Apart from the normal hazards, especially those involved in the extensive use of motor cars, many practitioners have suffered as the result of exceptional risks necessarily incurred in the course of their duties.

Acting on the instructions of Council, the Medical Insurance Agency has negotiated for the B.M.A., solely on behalf of its members home and overseas, a policy of insurance at an exceptionally low premium, which is notably free from restrictions and operates world-wide. This has only been achieved in the confident expectation of full support for the Scheme.

Death or Permanent Total Disablement

resulting from accident

£5 premium: £10,000 cover

for the maximum 10 *units per member—Separate units* 10*s. each*

Fatal Accident Only

£3.10s. premium: £10,000 cover

for the maximum 10 *units per member—Separate units* 7*s. each*

Immediate cover is available under this Scheme from any month in 1958 until December 31, 1959, at the proportionate premiums shown below:

For expiry on December 31, 1959

Month of Joining	PER UNIT	
	Full Cover	Fatal Accident Only
July 1958	15s.	10s.
August ,,	14s.	
September ,,	13s.	9s.
October ,,	12s.	
November ,,	11s.	8s.
December ,,	10s.	

Thereafter, the Scheme will operate from January 1 to December 31 each year to coincide with the B.M.A. membership year, but, subsequently, applications will be accepted at any time at proportionate rates to be quoted.

Attention is drawn to the full details of the Scheme in the advertisement on the preceding page.

MEDICAL INSURANCE AGENCY, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1

Medical News

Buckston Browne Dinner.—Sir JAMES PATERSON ROSS, P.R.C.S., presided at the Buckston Browne dinner, held at the Royal College of Surgeons on July 9. The toast to "The College" was proposed by Mr. DEREK WALKER-SMITH, who in some light-hearted remarks described after-dinner speaking as "all part of our puritan doctrine of after pleasure—pain." Mentioning the interest shown in the work of the College by the business world, Mr. Walker-Smith said that, in its broadest sense, the industrial future of the country depended on the health of the people, and that depended on the progress of medicine and surgery, which in its turn depended on research. In reply, Sir JAMES PATERSON ROSS said that the College was indebted to Sir George Buckston Browne for enabling it to undertake some of the most important work that had to be done to-day. Only a small number of people realized what research work was being done by the College: all of it had a practical application to medicine and surgery. It was of the utmost importance that research should be fruitful, so that its results might bring healing to all mankind. Proposing the health of the guests, among whom were many leaders of industry, Sir ARCHIBALD MCINDOE mentioned that, besides the President, three past-presidents of the College were present—Sir Harry Platt, Sir Cecil Wakeley, and Sir Hugh Lett, who was the son-in-law of Sir George Buckston Browne and one of the greatest friends the College had ever had. Replying to the toast Sir HARRY JEPHCOTT described the great influence the College had in building up medical schools overseas: its work was of great public as well as of medical importance.

Royal College of Surgeons.—At the council meeting on July 10 (see also p. 153) Dr. WARREN H. COLE, of Chicago, and Dr. CHARLES W. MAYO, of Minnesota, were admitted as honorary fellows. Dr. G. S. W. ORGANE was co-opted to the council as representing anaesthetics. Dr. I. W. MAGILL, Dr. R. J. MINNITT, Dr. E. S. ROWBOTHAM, Sir HENRY SOUTTAR, and Dr. R. M. WATERS were elected honorary fellows of the Faculty of Anaesthetists. Dr. H. J. WINDSOR, of Brisbane, was admitted to the fellowship as a member of 20 years' standing. The following professors, lecturers, and demonstrators were appointed for the ensuing year:

Hunterian Professors.—W. E. Tucker, R. A. Mogg, E. M. Nanson, J. B. Curtis, C. J. Kaplan, P. H. Jones, G. J. Hadfield, A. G. Parks, T. J. S. Patterson, J. W. Dickson, C. Havard, A. J. Davies, G. S. M. Botha, and J. S. Calnan.

Arris and Gale Lecturers.—E. R. Smith, G. L. Bourne, and K. M. Backhouse.

Erasmus Wilson Demonstrators.—R. Goodbody, K. M. Laurence, L. W. Proger, R. C. B. Pugh, H. A. Sissons, and M. O. Skelton.

Arnott Demonstrators.—J. Dobson, A. A. Barton, A. Howe, R. J. Last, R. M. Livingston, and B. Cohen.

King Edward's Hospital Fund.—At the Fund's 61st annual meeting in London on July 11, the DUKE OF GLOUCESTER, the president, reviewed some of the improvements the Fund had effected in hospitals during recent years. Grants had been used to provide amenities for patients and better living conditions for nurses; meals had been improved through the Catering Advisory Service and the School of Catering; much money had been spent on mental hospitals; and the influence of the three staff colleges—for ward sisters, future matrons, and hospital administrators—was leading to no less real results. Lord MCCORQUODALE, chairman of the management committee, drew attention to the inquiry into means of reducing unnecessary noise in hospitals. The treasurer, Lord ASHBURTON, said the Fund's capital was still £7m., in spite of the fact that since its inception 60 years ago the Fund had distributed over £16m. to the hospitals of London.

Birmingham Cancer Laboratories.—On July 4 Professor A. LACASSAGNE, of the Pasteur Radium Institute, Paris, opened new clinical research laboratories for the University Medical School in Birmingham. These laboratories, which have cost £50,000, were provided by the Birmingham Branch of the British Empire Cancer Campaign. They are situated on the site reserved for clinical research near to the Queen Elizabeth Hospital and the Medical School at Edgbaston, and will permit all research work on cancer carried on in Birmingham to be centred in one place. Professor JOHN ORR, professor of pathology in the University and director of cancer research, has been intimately concerned with this project. After the opening ceremony Professor L. SEVERI, of Perugia University, unveiled a plaque commemorating the work of Sir Gilbert Barling, the first chairman of the Birmingham Branch of the British Empire Cancer Campaign. A second plaque commemorating a gift from Alfred and Ruth Bullock towards the cost of the laboratories was then unveiled by Dr. O. MÜHLBOCK, of the Dutch Cancer Institute, Amsterdam.

Chair of Parasitology at Liverpool.—At a meeting of the University council on July 8 Dr. W. E. KERSHAW was appointed to the Walter Myers and Everett Dutton chair of parasitology and entomology upon the retirement of Professor R. M. GORDON. Dr. Kershaw graduated in medicine at Manchester University in 1935, proceeding M.D. in 1949 and D.Sc. in 1956. During the war he served in the R.N.V.R., first at sea and later as pathologist to the Royal Naval Auxiliary Hospital in Ceylon. In 1946 he was appointed lecturer in medical parasitology in the Liverpool School of Tropical Medicine, and Leverhulme senior lecturer in parasitology in 1957. He was awarded the Chalmers memorial gold medal of the Royal Society of Tropical Medicine and Hygiene in 1955, and was appointed to the council of that body in 1956. Dr. Kershaw will take up his new appointment on October 1.

New D.C.M.O. at Ministry.—Dr. D. THOMSON is to become a Deputy Chief Medical Officer at the Ministry of Health on October 1, on the retirement of Dr. G. A. CLARK. The other D.C.M.O. is Dr. G. E. GODBER. Before going to the Ministry of Health in 1946 Dr. Clark was professor of physiology and dean of the faculty of medicine at Sheffield University.

Monash University.—At its inaugural meeting on June 19 the interim council of the proposed Monash University in Victoria, Australia, decided that the new university should include a medical faculty. The Government of Victoria promulgated an Act in April to provide for the establishment of a second university in the State, to be named Monash University (after a former Chancellor of Melbourne University), and one of its purposes is to relieve those faculties at Melbourne University which already have to limit their intake of students. The medical members on the interim council are Professor MAURICE EWING, professor of surgery at Melbourne, and Dr. R. R. ANDREW, dean of the Alfred Hospital Clinical School.

Royal Society of Medicine.—Sir GEOFFREY MARSHALL has been elected president for the 1958–9 session. Other changes among the society's officers are that Professor R. H. S. THOMPSON succeeds Dr. G. W. S. ORGANE as an honorary secretary, and Mr. MYLES FORMBY and Dr. F. C. KELLY become honorary directors of photography in place of Professor K. J. FRANKLIN and Dr. D. A. MCDONALD. Sir CLEMENT PRICE THOMAS is the immediate past president.

Seventh International Congress of Leprology.—Arrangements to hold this quinquennial congress in New Delhi in November have unfortunately had to be cancelled at short notice. The Japanese Leprosy Foundation has offered, however, to hold it in Tokyo on November 12 under joint sponsorship with the International Leprosy Association. The secretary of the International Leprosy Association (8, Portman Street, London, W.1) urgently requests all who would be able to attend the congress in its new location to inform him at once.

"Biochemical Pharmacology."—This new quarterly from the Pergamon Press Ltd. is described as an international journal for research on the development of biologically active substances—particularly in the field of cancer chemotherapy—and their mode of action at the biochemical and sub-cellular level. Professor ALEXANDER HADDOW, F.R.S., is chairman of the editorial board, and the regional editors include Dr. P. ALEXANDER (executive editor) and Sir RUDOLPH PETERS, F.R.S. The first issue, dated July, 1958, contains original papers, short communications, and book reviews. Annual subscription (including postage) is £6 per volume (£5 5s. if for personal use). The publishing offices are at 425, Fitzroy Square, London, W.1.

Light Diets.—The Hospital Catering Advisory Service of King Edward's Hospital Fund has issued a memorandum on "Light Diets." It is designed to help catering officers or housekeeping sisters fulfil prescriptions for light diets. Copies of the memorandum are obtainable (price 1s., post free) from the Fund's officers, 34, King Street, London, E.C.2.

Bristol University.—Dr. J. CLUTTON-BROCK has been appointed lecturer in anaesthetics and head of the department of anaesthesia. Dr. SUZANNE CLARKE has been appointed lecturer in bacteriology.

Aberdeen University.—At the graduation ceremony on July 4 the University's honorary D.D. was conferred on the Reverend Dr. A. C. IRVINE, senior missionary of the Church of Scotland Mission in Kenya.

Film Award.—A film on congenital obstruction of the bladder neck, made by Mr. D. I. WILLIAMS, Dr. D. EDWARDS, and the film unit of the Institute of Urology, London, was awarded a silver medal at the International Congress of Urological Films in Brussels last month.

COMING EVENTS

Royal Microscopical Society.—Exhibition of photomicrographs, July 23–30, at the Polytechnic School of Photography, 309, Regent Street, London, W.1. Open to non-fellows of the society (admission free) after opening day (July 24 and 29, 10 a.m. to 10 p.m.; other days, 10 a.m. to 4 p.m.).

Cambridge University Postgraduate Medical School.—Course on "Progress in the Biological Sciences in Relation to Dermatology," September 22–27, at Cambridge. The course is intended primarily for practising dermatologists. Details from the Secretary, the Medical School, Tennis Court Road, Cambridge.

NEW ISSUES

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Annals of the Rheumatic Diseases.—Issued quarterly (£3 annually). The new issue, Vol. 17, No. 2, includes:

PREDNISONE IN RHEUMATOID ARTHRITIS: METABOLIC AND CLINICAL EFFECTS. L. Emmerson Ward, Howard F. Polley, Marschelle H. Power, Harold L. Mason, Charles H. Slocumb, and Philip S. Hench.
GENETIC STUDIES ON RHEUMATOID ARTHRITIS. J. S. Lawrence and J. Ball.
ARTHRITIS ASSOCIATED WITH ULCERATIVE COLITIS. E. G. L. Bywaters and B. M. Ansell.
EFFECT OF LONG-TERM TREATMENT WITH CORTICOSTEROIDS ON ADRENOCORTICAL FUNCTION. F.-E. Krusius and Martti Oka.
RADIOSODIUM CLEARANCE FROM THE KNEE JOINT IN RHEUMATOID ARTHRITIS. R. Harris, J. B. Millard, and S. K. Banerjee.
OBSERVATIONS ON THE SHRINK TEMPERATURE OF COLLAGEN AND ITS VARIATIONS WITH AGE AND DISEASE. Patricia C. Brown, R. Consden, and L. E. Glynn.
CLINICAL FEATURES AND COURSE OF ANKYLOSING SPONDYLITIS. M. Wilkinson and E. G. L. Bywaters.
MEASUREMENT AND INTERPRETATION OF SYNOVIAL FLUID VISCOSITIES. C. H. Barnett.
ESTIMATION OF THE ERYTHROCYTE SEDIMENTATION RATE OF CAPILLARY BLOOD. H. E. D. Lloyd.
RELATION BETWEEN THE AFFINITY FOR CONGO RED AND THE GLYCOPROTEIN CONTENT OF SERUM IN RHEUMATOID ARTHRITIS AND RELATED DISEASES. Børge Larsen.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue, Vol. 42, No. 7, includes:

EFFECT OF CERVICAL SYMPATHOTOMY ON AN OCULAR RESPONSE TO HYPOTHALAMIC STIMULATION. J. Gloster and D. P. Greaves.
OPHTHALMIC DISEASE IN HONG KONG. G. C. Dansey-Browning.
PROTECTION OF THE GRAFT WITH CONDOM IN KERATOPLASTY. A. Miklós and L. Masovszky.
REPLACEMENT OF TRAUMATIC IRIS PROLAPSE. R. Stein.
DOMINANTLY INHERITED OPTIC ATROPHY. Ruby Joseph and J. B. Davey.
INCOMITANT STRABISMUS OF UNUSUAL ORIGIN. M. S. Nirankari and M. C. Maudgal.
INFECTION WITH MICROCOCCUS TETRAGENUS AS A COMPLICATION OF PENETRATING KERATOPLASTY. G. J. Romanes.
"AMYLOID TUMOUR" OF THE EYELIDS. S. Agarwal and J. B. Shrivastav.
TWO CASES FROM MALAYA. B. M. McOwan.
OCULAR CASES OF MEDICAL INTEREST. J. Horton Young.
REFRACTION IN MARKED PTOSIS AND BLEPHAROCHALASIS. J. D. Magor Cardell.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, July 22

SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., 6th Kelynack Memorial Lecture by Dr. M. H. J. Krauweel (Amsterdam): Incidence and Treatment of Alcoholism in the Netherlands.

Wednesday, July 23

●INSTITUTE OF CHILD HEALTH.—5 p.m., Simpson Smith Memorial Lecture by Dr. Willis J. Potts (Chicago): Congenital Atresia of the Oesophagus.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. Janet S. F. Niven: Cytopathological Aspects of Latent Infection.

Thursday, July 24

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Hospital for Tropical Diseases, 7.30 p.m., clinical meeting.
WEST LONDON HOSPITAL MEDICAL SCHOOL.—5 p.m., Alex Simpson Smith Memorial Lecture by Mr. Harold Burge: Problems in Gastric Surgery.

Friday, July 25

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. W. P. Cleland: clinical demonstration.
●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.—5 p.m., William Meredith Fletcher Shaw Memorial Lecture by Professor James Black: Reminiscences of Fifty Years' Medical Practice—Forty-seven of Them in South Africa.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.30 p.m., Moynihan Lecture by Dr. Willis Potts: Respiratory Emergencies in the Newborn.

APPOINTMENTS

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—D. E. Savage, M.B., F.R.C.S., M.R.C.O.G., Gynaecologist, Highlands General Hospital; A. Knudsen, M.D., M.R.C.P., Pathologist, West Middlesex Hospital; R. C. Fuller, M.B., F.R.C.S., Surgeon, Acton Hospital; J. C. MacKillop, M.B., F.F.Hom., Homoeopathic Physician, Royal London Homoeopathic Hospital; Margaret D. W. Hamilton, M.B., F.F.A. R.C.S., Anaesthetist, Willesden General Hospital.
WRIGHT, J. T., D.M., M.R.C.P., Part-time Consultant Physician to the London Hospital, Whitechapel, E.

BIRTHS, MARRIAGES, AND DEATHS

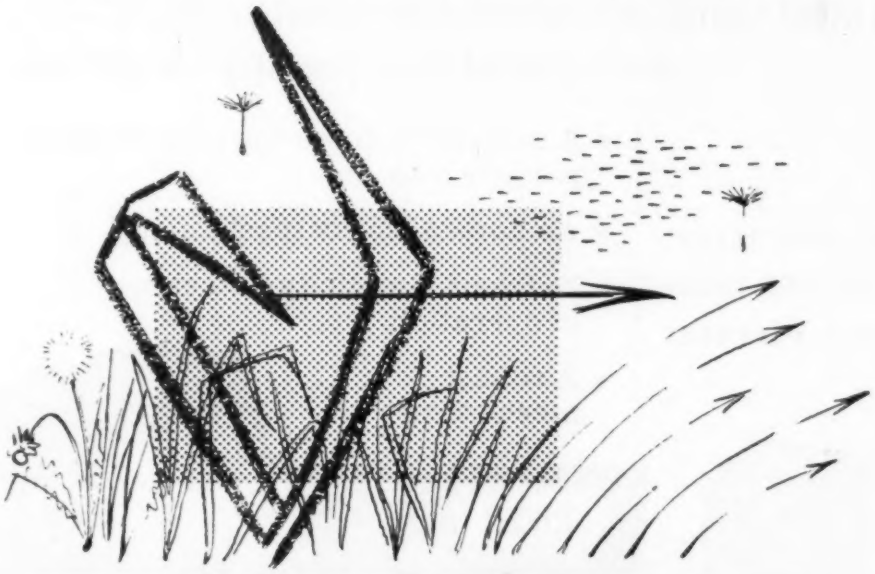
BIRTHS

Carrick.—On July 4, 1958, to Muriel and David Carrick, M.R.C.S., L.R.C.P., of Feering House, Kelvedon, Essex, a daughter—Eugènie Sarah Anne.
Dhanji.—On June 20, 1958, at 27, Belle Vue Terrace, Sandbach, Cheshire, to Iris (formerly Lewis), wife of Dr. Noor Ali Dhanji, a daughter—Judith Soraya.
Dunn.—On July 5, 1958, at home at Bridgnorth, to Sylvia (formerly Matheson), M.B., B.S., and Andrew Dunn, L.D.S., a son—Conal Matheson.

DEATHS

Bell.—On July 4, 1958, Henry Cooke Bell, M.M., L.R.C.P.&S.I. & L.M., of The Paddock, Weston-on-Trent, near Derby, aged 64.
Crichton.—On June 27, 1958, James Smith Crichton, M.B., Ch.B., of 9, Addison Crescent, Kensington, London, W.
Dunn.—On June 27, 1958, at his home, Fern Hill, Manchester Road, Burnley, Lancs, William James Dunn, M.D.
Dyson.—On June 28, 1958, Harold Edward Dyson, M.D., of Stonecarre, Hosey Hill, Westerham, Kent, formerly of Wembley, Middlesex.
Hudson.—On July 11, 1958, Major-General Corrie Hudson, C.B., C.I.E., D.S.O., F.R.C.S.Ed., of Garth Knowle Drive, Sidmouth, Devon, aged 84.
Jackson.—On June 21, 1958, at his home, 96, Lowther Road, Bournemouth, Hants, Thomas Sparks Jackson, M.R.C.S., L.R.C.P., aged 95.
Jordan.—On June 27, 1958, at her home, near Lechlade, Glos., Helen Rosaline Jordan (formerly Ashton), M.B., B.S., aged 66.
Macdonald.—On July 2, 1958, at Feltwell, Norfolk, Alexander Lamont Macdonald, M.B., Ch.B.
Smith.—On June 25, 1958, Edward Archibald Smith, M.B., Ch.M., F.R.C.S., of Eastfield House, Wells, Somerset, late of Vancouver, British Columbia, aged 83.
Smith.—On June 26, 1958, at Monmouth, Herbert Smith, M.R.C.S., L.R.C.P., D.T.M., aged 68.
Smith.—On June 21, 1958, at Bromley, Kent, Fleet Floyd Strother Smith, M.D., Colonel, I.M.S. (retired), aged 74.
Streatfeild.—On July 2, 1958, in hospital, London, William Hugh Raymond Streatfeild, M.R.C.S., L.R.C.P., of 18a, Thurloe Place, London, S.W., aged 79.
Swan.—On June 22, 1958, James Douglas Carnon Swan, M.B., Ch.B., of 370, Dorchester Road, Weymouth, Dorset.
Tuohy.—On June 29, 1958, at a nursing-home, Patrick Gerald Tuohy, M.B., Ch.B., of Shornbrook, Crowborough, Sussex, aged 70.

In hay fever and perennial vasomotor rhinitis



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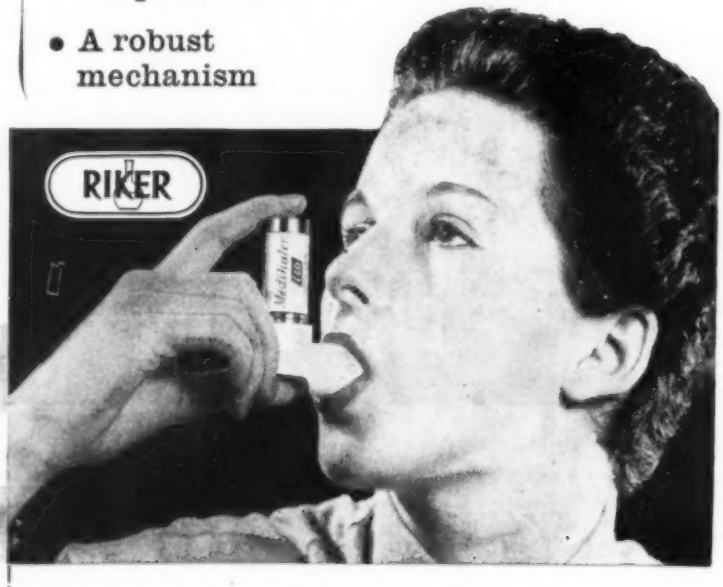

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Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Chemotherapy for Pulmonary Tuberculosis

Q.—*What is the optimum dosage of streptomycin and isoniazid for patients suffering from pulmonary tuberculosis with positive sputum and high E.S.R.?*

A.—The optimum dosage for patients under the age of 40 is streptomycin sulphate 1 g. in one injection daily together with isoniazid 100 mg. twice daily. This should be continued at least until three sputum cultures are known to be negative, when P.A.S. with isoniazid can be substituted. It is safer still to initiate treatment with all three drugs until the patient's organisms are known, by laboratory testing, to have been initially sensitive to all three drugs. Otherwise isoniazid resistance may emerge in the occasional patient who has had the misfortune to be infected with streptomycin-resistant organisms, or vice versa. In any case chemotherapy should continue for at least a year after sputum conversion. Streptomycin should not be given every three days with daily isoniazid : with this regime resistant tubercle bacilli will emerge in 10 to 15% of cases.[1] In patients over the age of 40 daily streptomycin is apt to give rise to vestibular upset. These patients can be given streptomycin three times weekly, but then in that event both isoniazid *and* P.A.S. (5 g. of the sodium salt twice daily by the mouth) must be given if drug resistance is to be avoided. Streptomycin is more likely to give rise to vestibular upset, dihydrostreptomycin to deafness. Dihydrostreptomycin deafness may be permanent. At least partial recovery from vestibular upset is usual, especially if streptomycin is stopped as soon as the patient complains of giddiness. Streptomycin is therefore preferable to dihydrostreptomycin. For details of chemotherapy the *Textbook of Medical Treatment*, edited by Dunlop and his colleagues,[2] may be consulted.

REFERENCES

1 M.R.C. Report, *Brit. med. J.*, 1955, **1**, 435.
2 *Textbook of Medical Treatment*, 1958, edited by D. M. Dunlop, Sir Stanley Davidson, and S. Alstead. E. and S. Livingstone, Edinburgh.

Antibiotic Antagonism

Q.—*Since tetracyclines may antagonize the action of penicillin, is it inadvisable to give systemic penicillin at the same time as local tetracycline therapy?*

A.—Antagonism between penicillin and tetracyclines is a reality, but strictly conditioned by the concentrations of the two antibiotics. Thus it is demonstrable in the treatment of acute infections in mice only when the dose of each antibiotic is near the minimum effective level, and the only clear illustration of it on record in the clinical field was in the treatment of meningitis, when neither antibiotic was administered intrathecally, and the concentration attained by each in the cerebrospinal fluid must have been at a critically low level.

The mechanism of this effect, when it occurs, is interference with the bactericidal action of penicillin—which is exerted only on multiplying bacteria—by an antibiotic which is bacteriostatic—i.e., prevents multiplication. It is a purely one-way effect : penicillin does not interfere with the action of a tetracycline when the latter is present in a concentration in excess of that necessary for independent effect. There is thus no objection to the treatment specified in the question : the high concentration of tetracycline produced by local application—say, to the eye—would be unaffected by any penicillin in the lacrimal secretion. On the other hand, so little tetracycline would be absorbed that any antagonistic combined effect in the body generally would be most unlikely.

Determining Immunity to Poliomyelitis

Q.—*May the usual serum tests—precipitation, complement fixation, or virus neutralization—be used to determine immunity to poliomyelitis?*

A.—Antibodies to the three types of poliomyelitis virus may be detected by either neutralization, complement fixation, or flocculation. The last method is experimental and has not been accepted as a routine method.[1] Following infection, specific complement fixing and neutralizing antibodies can easily be detected, but the former fall off much quicker than the latter and will not be found in the absence of neutralizing antibodies.[2] The neutralization test is therefore the best method of detecting whether a person is immune to poliomyelitis or not. Subjects without antibody must be considered susceptible, although a small proportion of these may in fact be immune as their antibody may be below the detectable level. Detectable antibody to any given type indicates prior infection with, and therefore immunity to, that type but not to the other two, although heterologous antibody may reduce the incidence of clinical disease in some instances. The routine tests in use for detecting neutralizing antibodies are time-consuming and expensive, and attempts have been made to introduce simpler techniques.[3] Unfortunately a reliable skin test is not yet available.

REFERENCES

1 Lennette, E. H., and Schmidt, N. J., *Amer. J. Hyg.*, 1957, **65**, 210.
2 Smith, W., Sheffield, F. W., Churcher, G., and Lee, L. H., *Lancet*, 1956, **2**, 163.
3 Salk, J. E., *J. Amer. med. Ass.*, 1956, **162**, 1451.

N-acetyl-p-aminophenol

Q.—*N-acetyl-p-aminophenol is being advertised now as a substitute for aspirin. Is this, like most aniline derivatives, a substance likely to cause agranulocytosis?*

A.—N-acetyl-*p*-aminophenol may also be called *p*-hydroxy-acetanilide, which shows that it is closely related to *p*-ethoxyacetanilide or phenacetin. It may be regarded as a variant of phenacetin. While acetanilide has some reputation for causing agranulocytosis, though much less than has aminopyrine, phenacetin has rarely been known to do so.[1] The substances which cause agranulocytosis include the sulphonamides and thiouracil ; it is very difficult to indicate what chemical groups are responsible. All probably act because they resemble compounds occurring in the body whose place they usurp.

REFERENCE

1 Kracke, R., and Parker, F. P., *J. Lab. clin. Med.*, 1933, **19**, 799.

Simple Retroversion

Q.—*What is the treatment for a simple symptomless retroversion of the uterus found at post-natal examination?*

A.—A symptomless, simple (i.e., mobile) retroversion found post-natally needs no treatment unless it is associated with obvious subinvolution—in which case correction and the insertion of a pessary to maintain the new position for six weeks are advisable. In nearly all women with simple post-natal retroversion the uterus was in that position before pregnancy. A patient who has been told she has a retroversion should be assured that it is normal for her.

X-ray Sterilization of Bone Grafts

Q.—*Is it possible to use x rays for sterilizing bone for storage and subsequent grafting?*

A.—A good deal of experimental work is being done on the use of *x* rays for sterilization, particularly in the canning industry. No definitive conclusions have yet been reached which would lead one to expect *x* rays to be used for a like purpose in medicine. In any case radiation is no respecter of cells, and if a dose lethal to an organism is applied it will also presumably ensure the death of the cells in the tissue upon which the organisms lie. In the case of homografts, which, unlike autogenous grafts, are not, in fact, grafts but implants, their contained cells apparently

play no part in the incorporation into the host, and any simple and non-specific form of sterilization would be suitable.

Notification of Industrial Dermatitis

Q.—*Are there any regulations for reporting industrial dermatitis?*

A.—H.M. Factory Inspectorate of the Ministry of Labour and National Service is concerned with the prevention of dermatitis in establishments under the Factories Acts, and expert advice, including that from the medical branch, is available to any employer.[1] Dermatitis is not a notifiable industrial disease under the Factories Acts, but, with certain qualifications, occupational dermatitis is prescribed for injury benefit under the National Insurance (Industrial Injuries) Act.[2]

REFERENCES

1 *Dermatitis in Industry with Special Reference to Barrier Substances.* H.M. Stationery Office Form 330.
2 *Notes on the Diagnosis of Occupational Diseases Prescribed under the National Insurance (Industrial Injuries) Act, 1946.* H.M. Stationery Office. Price 1s. 6d.

Thermometer Hygiene

Q.—*What is a proper technique for thermometer hygiene when recording a number of temperatures in the course of a round of visits?*

A.—When temperatures are taken in the axilla, which is perhaps preferable in the circumstances, there is little risk of transmitting infection unless from a patient with an infective dermatitis in that area. Oral use clearly demands that a reliable process of disinfection be regularly employed. The most comprehensive study of this problem was made by Frobisher, Sommermeyer, and Blackwell.[1] They considered several classes of germicide unsuitable for various reasons, and found others, which are credited with high activity in other types of use, to be ineffectual. Their best results in disinfecting glass rods or actual thermometers contaminated with tubercle and diphtheria bacilli, staphylococci, and streptococci were obtained with 70% ethyl or isopropyl alcohol, the latter being rather more effective. The results were improved by preliminary wiping on cotton-wool wet with a mixture of equal parts of tincture of green soap and 95% ethyl alcohol. If this is done, carrying a thermometer in a case containing spirit of the right concentration should evidently be safe, but it would be advisable to renew the contents frequently.

REFERENCE

1 Frobisher, M., Sommermeyer, L., and Blackwell, M. J., *Appl. Microbiol.*, 1953, **1**, 187.

A.I.H. in "Normal" Partners

Q.—*What part can artificial insemination, using the husband as donor, play in the treatment of infertility when both husband and wife are apparently normal? Is the chance of conception increased when the semen is placed in the uterus instead of in the vagina?*

A.—A.I.H. has no place in the treatment of infertility when both husband and wife are apparently normal and when coital effectiveness has been demonstrated by a satisfactory post-coital test. However, since this important test is so often omitted in the so-called investigation of infertility as generally practised outside special fertility clinics, it is possible that the apparently normal husband and wife referred to do not have mechanically effective intercourse. If appropriate investigation shows this to be the case, and advice intended to improve coital technique still fails to produce a satisfactory post-coital test, then clearly A.I.H. would be a logical procedure to recommend. Nevertheless, early conception after resorting to A.I.H. in cases of this kind is the exception rather than the rule.

Adequate data on which to base an answer to the second part of the question are not available. Such as exist do not suggest that superior results from A.I. necessarily follow intrauterine insemination, except, of course, when cervical hostility is the reason for using A.I. By cervical hostility is meant the condition in which the cervical secretions, by reasons of their quality, quantity, or both, do not permit the passage of spermatozoa through them. This is a commonly encountered finding in subfertile couples and frequently defies attempts at treatment. In such cases the object is to place some spermatozoa above the cervical block in the hope that they will then be able to proceed through the uterus and tubes.

NOTES AND COMMENTS

Toxicity of "Albamycin."—Dr. A. R. H. HICKS (medical adviser, Upjohn of England Ltd., Crawley, Sussex) writes: I have read with some concern the answer of your expert to the question, "Does albamycin (calcium salt of novobiocin) have a toxic effect on the liver?" ("Any Questions?" June 21, p. 1493). The occurrence of diffuse hepatic necrosis in the case cited by Bridges *et al.*[1] is possibly attributable to novobiocin, but it must be considered in relation to the dose of novobiocin which the patient received. The boy, aged 14 years, received 2 g. novobiocin 12 hourly, orally for eight days. The weight of the boy is not given but is unlikely to be more than 50 kg. He received, therefore, about 80 mg. per kg. of body weight daily for eight days—more than five times the recommended dose (15 mg. per kg. of body weight daily). A report from the Upjohn Company (presumably Larson *et al.*[2]) is quoted as describing the occurrence of severe degenerative changes in the liver and kidneys in dogs receiving 300 mg. albamycin per kg. of body weight daily. These changes were only noted when doses of 300 mg. were given intravenously for five days. When the same dose was given orally no degenerative changes in the liver or kidneys were observed at necropsy. Welch *et al.*[3] report on a series of 208 adult males who were given 10 g. novobiocin over a 12-day period. Only one of these exhibited a drug rash and three of them showed a yellow discoloration of the sclerae which faded gradually on discontinuation of the drug. By now many thousands of patients have received albamycin and the many reports which have been published demonstrate conclusively that it is an effective drug and that its use, in the recommended dosage, is accompanied by but few side-effects—most of these being insignificant clinically. To my knowledge there has been no further reference to any toxic effect on the liver. If potent drugs are given in doses greatly in excess of those recommended by the manufacturers it is not unlikely that disasters will occur from time to time, and it is not unreasonable to assume that novobiocin could have been responsible for the pathological changes described earlier. However, the omission of details concerning the unprecedented high dosage employed must have given a very false impression of albamycin, a drug which wide usage has shown to be extremely useful and safe in the normally accepted dose range.

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1 Bridges, R. A., Berendes, H., and Good, R. A., *J. Pediat.*, 1957, **50**, 579.
2 Larson, E. J., *et al.*, *Antibiot. and Chemother.*, 1956, **6**, 226.
3 Welch, H., Lewis, C. N., Putnam, L. E., and Randall, W. A., *Antibiot. Med.*, 1956, **3**, 27.

Correction.—The obituary of Dr. Anna M. Williams (June 14, p. 1423) stated that she was born abroad. She was, in fact, born in Edinburgh, and up to the time of graduation she spent nearly all her life in Scotland.

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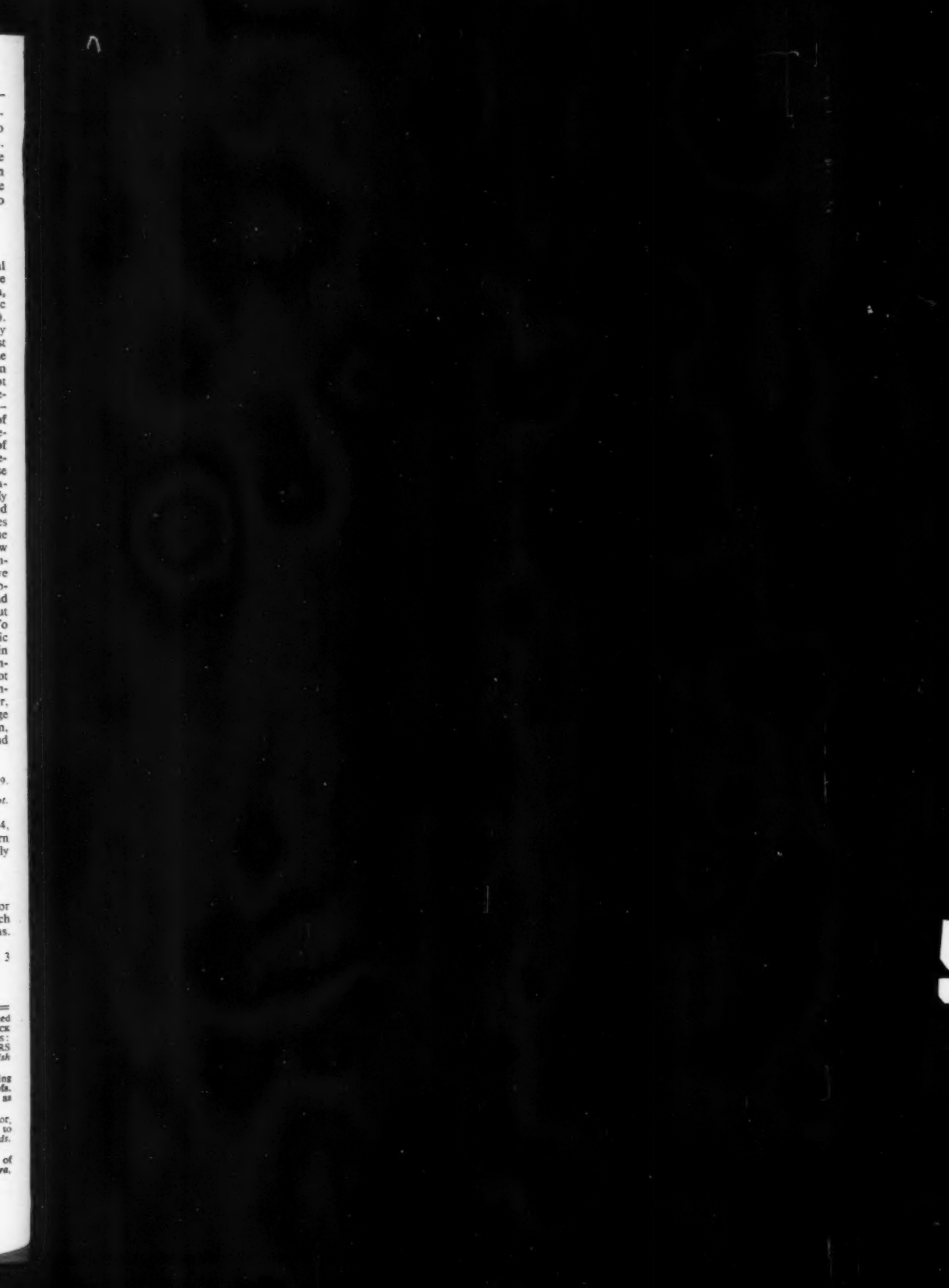
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